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# Copper(I)-Catalyzed Selective Synthesis of Fluorine-Containing Organoboron Compounds and their Applications

**Sota Akiyama**

**2020**

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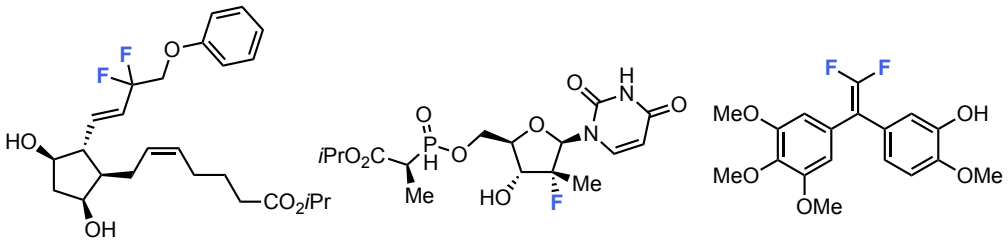
Acknowledgments

# General Introduction

## 1. Organofluorine Compounds

The introduction of fluorine atom(s) into small molecules can greatly be perturbed for the chemical, or physical properties of the compounds, thus an array of compounds bearing fluorine atom(s) has been utilized in material and medicinal chemistry.[1] For example, fluorine atom substituents can increase the metabolic stability by the effect of strong C–F bond, without effect for steric properties because of the similarity in van der Waals radius to hydrogen in organic molecules. Especially, the fluorinated bioactive compounds have widely been used, as 20% of pharmaceuticals and 35% of agrochemicals on the market are the compounds containing fluorine atom(s) (Figure 1)[2]

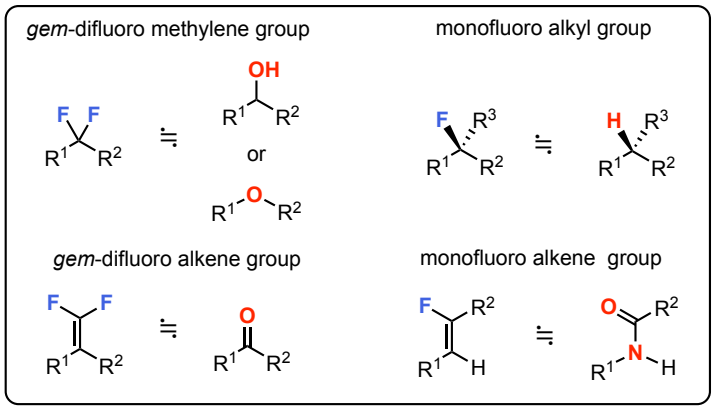
***Figure 1.*** Representative Examples of Bioactive Fluorine-containing molecules




***Tafluprost*** ***Sofosbuvir*** ***Antitubulin agent***

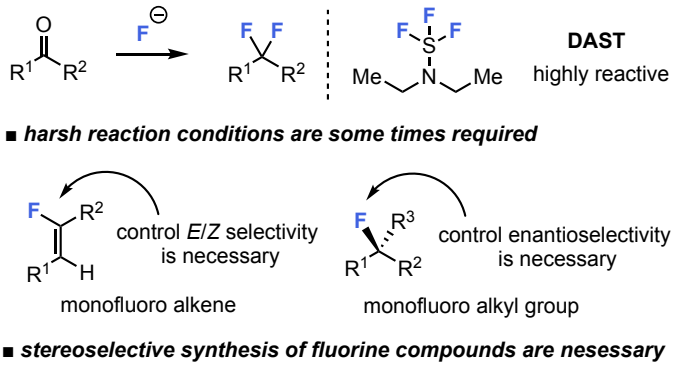
Additionally, the several fluorine moieties can be used as the bioisostere of functional groups by taking advantage of the unique features of fluorine atoms (Figure 2). For example, the *gem*-difluoro methylene group acts as a lipophilic mimic for a single oxygen atom such as alcohols and ethers.[3] For the same reasons, *gem*-difluoro alkenes can replace the single oxygen atom in carbonyl groups.[4] The monofluorinated compounds are also considered as the substitute unit of functional groups; the monofluoro alkyl group acts as a single hydrogen atom due to the similar size, as well as the monofluoro alkene as an amide group due to similar electronic properties.[5]

***Figure 2.*** Fluorine moieties become bioisostere of several functional groups




Although these unique features of fluorine moieties intrigue to apply them broad applications, there are some problems for their synthesis (Figure 3). One of the significant problems is the lack of mild reaction conditions for their selective synthesis. For instance, conventional approaches for preparing difluoro methylene group include deoxyfluorination of ketones, despite some functional groups cannot endure under these reaction conditions because the fluorination reagents such as DAST are highly reactive.[6] Further, another problem is the general difficulty in the control of the stereoselectivity of monofluoro compounds, which is inevitable to use them as bioisostere for amide or a hydrogen atom.[5a] From the point of these views, the development of methods for the selective synthesis of these fluorine-containing compounds under a mild condition is still highly desired.

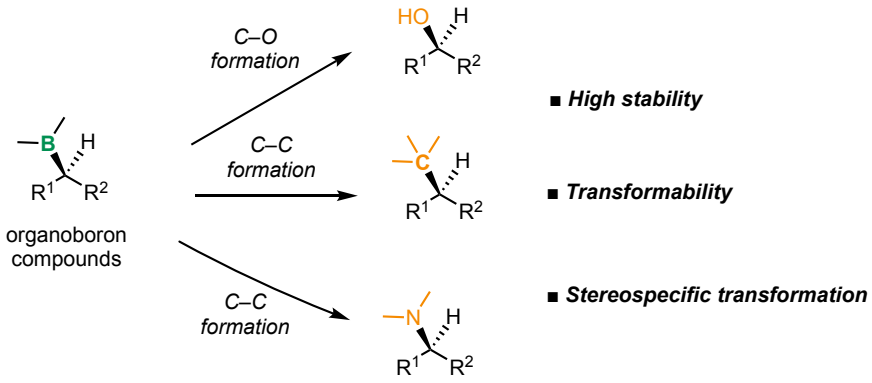
***Figure 3.*** The problems for the synthesis of fluorine compounds



## 2. Organoboron Compounds

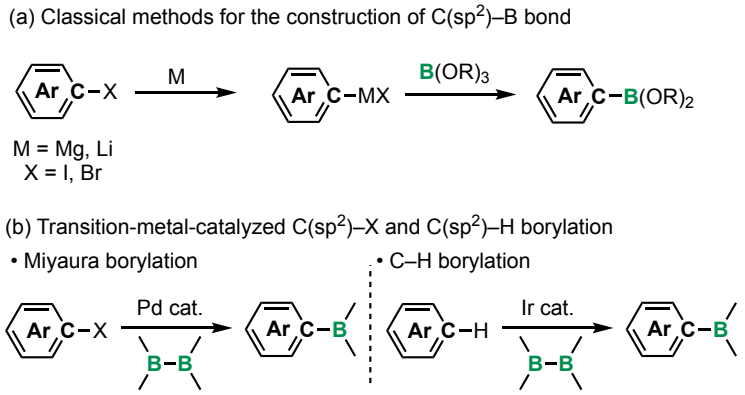
Organoboron compounds are undoubtedly versatile synthetic intermediate due to their transformable ability. Especially organoboronic ester, normally show reasonable stability under normal atmospheric conditions, which is largely different from many organometallic compounds such as Grignard reagents and organolithium compounds that require careful handling in their usage and storage. These stable organoboronic esters are also sufficiently reactive for use in organic synthesis with an appropriate activation procedure. Additionally, enantioenriched organoboron compounds are recognized as important chiral building blocks because these compounds are potentially applicable for C–O, C–N, and C–C bond formation with retention of their stereogenic centers (Figure 4).[7]

***Figure 4.*** The utility of organoboron compounds



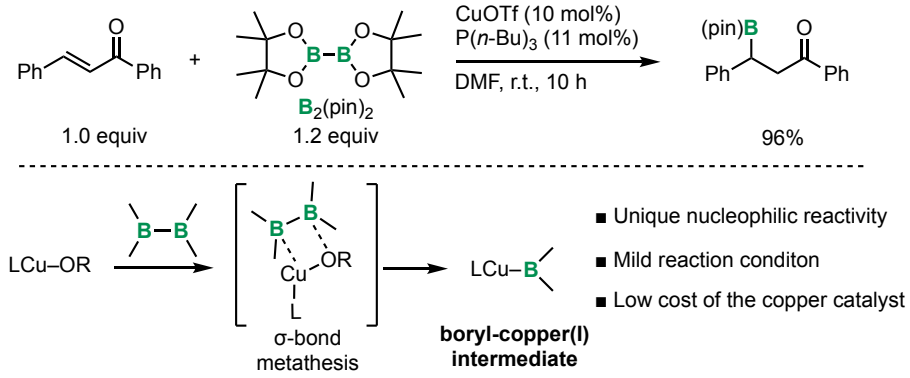

Because of the utility of organoboron compounds, methods for the synthesis of these compounds are of considerable current interest. Classically, these compounds, especially the compounds bearing a C($sp^2$)–B bond, are prepared via the reaction of hard organometallic reagents with electrophilic boron precursors such as borate esters (Scheme 1a), although such methods have relatively limited substrate scope due to the poor functional group tolerance.[8] For those reasons, transition-metal-catalyzed C($sp^2$)–H and C($sp^2$)–X borylation strategies have emerged recently for the synthesis of arylboronates or alkenyl boronates (Figure 1b).[9]

***Scheme 1.*** Example of classical C($sp^2$)–B bond formation and transition-metal-catalyzed C($sp^2$)–H or C($sp^2$)–X borylation via Miyaura-Ishiyama-Hartwig borylation



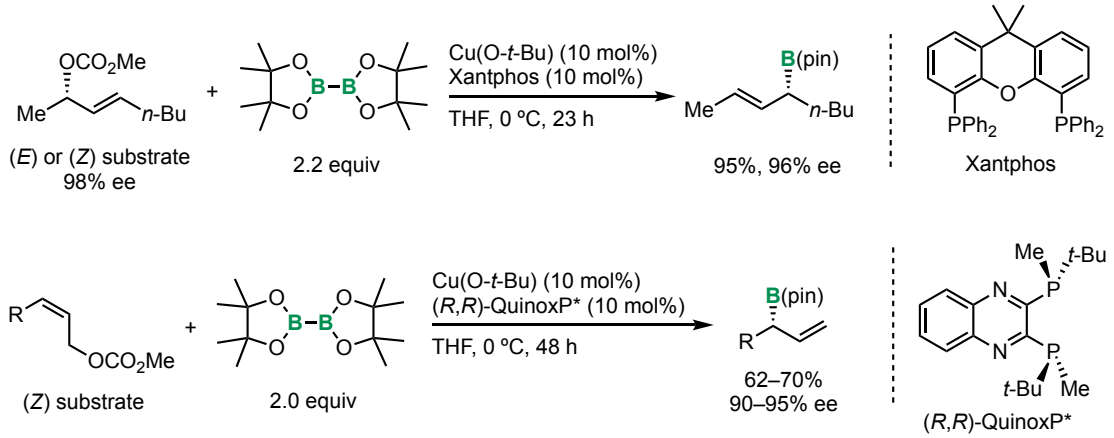

Along these lines, processed mediated by a boryl-copper species are particularly attractive enabled by mild reaction conditions, good functional group tolerance, and low cost of the metal catalyst. The first examples of the copper(I)-catalyzed borylation reaction of α,β-carbonyl compounds by using copper(I)/diboron catalyst system reported by Hosomi and Ito group, and Miyaura and Ishiyama group independently (Scheme 2).[10,11] In this reaction, the boryl(I)-copper intermediate was generated by the σ-bond metathesis between copper(I) species and diboron reagent. This metal-boryl complex has useful nucleophilic reactivity with high stereoselectivity for many borylation reactions.

***Scheme 2.*** The first example of copper(I)-catalyzed borylation reaction of conjugated enone



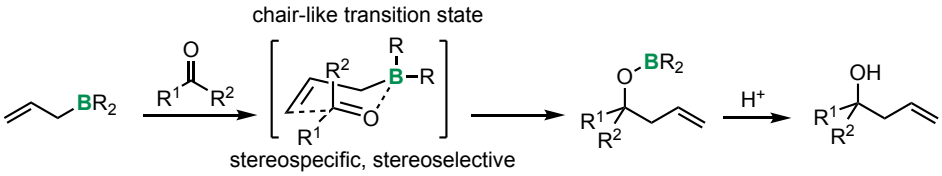

Since 2005, Ito and Sawamura group reported many asymmetric or non-asymmetric borylation reactions by using this borylcopper(I) intermediate. For example, they have reported a regio- and stereospecific allylic boryl substitution of allyl electrophiles with copper(I)/Xantphos catalytic system (Scheme 3).[12] Further, enantioselective boryl substitution of allyl carbonates via enantioselective insertion of boryl-copper(I) intermediate with a chiral ligand toward olefins followed by copper(I)-carbonate elimination have been developed by the same authors.[13]

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



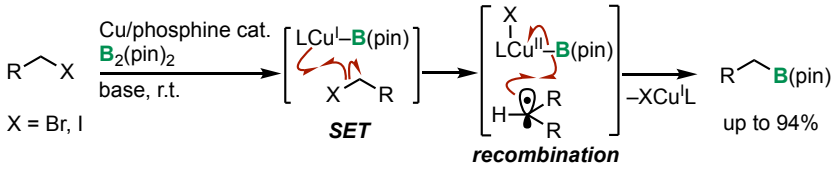

The compounds, which are the allylboronates, obtained in this reaction can be used as an allylation reagent for carbonyl compounds or imines.[8] This reaction proceeds via chair-like transition states by the effect of Lewis acidic ability of the boron atom. Concerted activation of the oxygen atom on the carbonyl moiety and subsequent nucleophilic attack from the γ-carbon in the C=C bond to the carbon atom on the carbonyl moiety would occur in the transition state, which involves tightly constrained transition state, resulting in the high stereoselectivity (Scheme 4).

***Scheme 4.*** Allylation of carbonyl compounds with allylboronates



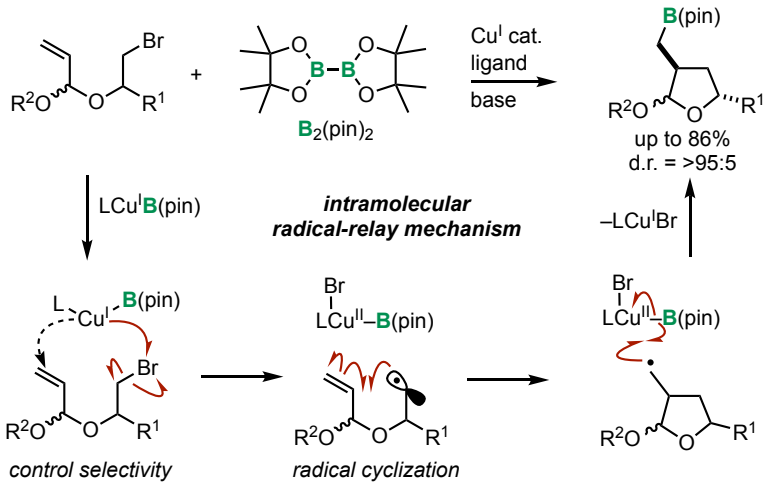

In 2012, Ito and Marder groups independently reported the copper(I)-catalyzed boryl-substitution reaction with unactivated alkyl halides to give the corresponding boryl-substitution products. The reaction would proceed via single electron transfer (SET) between boryl copper(I) intermediate to generate the alkyl radical species, followed by radical recombination with boryl(II) copper intermediate to afford the boryl-substitution products, as indicated by radical-clock experiments (Scheme 5).[14]

***Scheme 5.*** Boryl-substitution of alkyl halides via a radical mechanism




After these seminal works, Ito group also reported the borylative radical cyclization reaction in 2018. In this reaction, the boryl(I)-copper intermediate can react with both the alkene and halide moieties. This possible two reactivities were controlled by choice of proper ligand. For the cyclization reaction, the intramolecular radical-relay mechanism was proposed. The cyclization products have a transformable alkylboronate moiety with high diastereoselectivity (Scheme 6).[15]

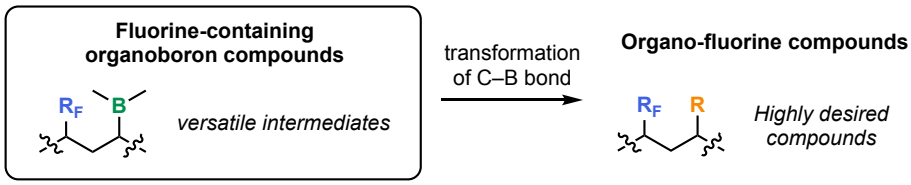
***Scheme 6.*** Copper(I)-catalyzed borylative radical cyclization via the intramolecular radial-relay mechanism



## 3. Fluorine-Containing Organoboron Compounds

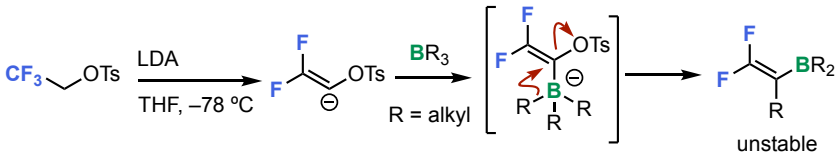
As I described above, the effective methods and versatile fluorinated-building blocks for the preparation of fluorine compounds are still highly desired. For this purpose, the fluorine-containing organoboron compounds have attract attention recently because of the transformability of organoboron compounds which result in access for the highly desired fluorine compounds (Figure 5).

***Figure 5***. The utility of fluorine-containing organoboron compounds



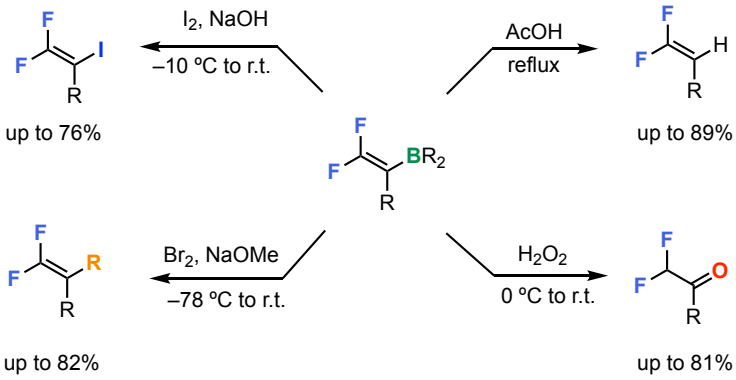

The pioneering work for the synthesis of fluorine-containing organoboron compounds has been developed by Ichikawa group in 1989 (Scheme 7).[16] They used the β-$CF_3$ p-toluenesulfonate as a substrate and generated β,β-*gem*-difluoro-α-tosyloxyvinylanion by the reaction with LDA. This species reacted with alkyl boranes followed by 1,2-migration of the alkyl group from the boron atom on the vinylic carbon to afford the β,β-*gem*-difluoroalkenylborane.

***Scheme 7***. Pioneering work for the synthesis of fluorine-containing organoboron compounds



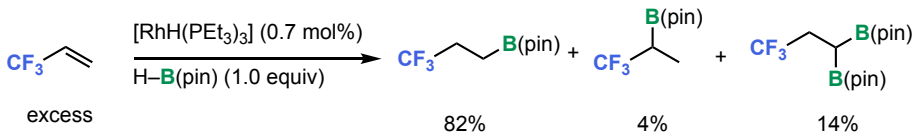

Although a β,β-*gem*-difluoroalkenylborane is unstable, this compound can transform interesting fluorinated compounds (Scheme 8).[17] For example, the *gem*-difluoroalkenylborane undergo protonolysis by the treatment with acetic acid. Additionally, oxidation of the C–B bond by adding an aqueous solution of $H_2O_2$ provided the corresponding difluoromethyl ketones in high yield. The reaction of vinyl boranes with $I_2$ is also an attractive method for obtaining the related iodo compounds. Contrary, 1,1-difluoro-1-alkenes was obtained by the reaction with bromine and NaOMe via 1,2-migration of β-alkyl group.

***Scheme 8***. Transformations of β,β-*gem*-difluoroalkenylborane



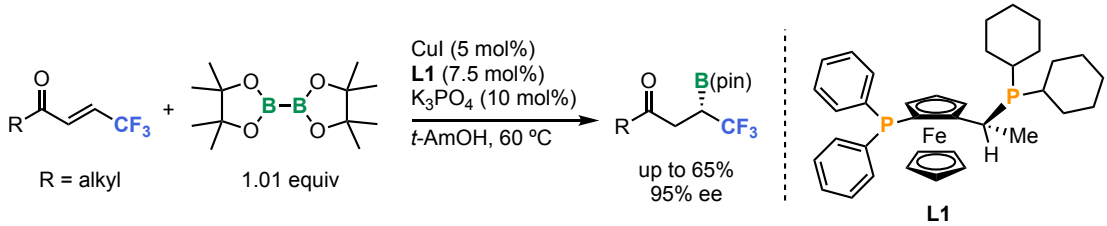

The reaction is interesting and useful; however, the use of the stoichiometric amount of alkali metal reagent, which led to narrow the substrate scopes due to the low functional group tolerance. Taken that, recently, a transition metal-catalyzed borylation for the fluorinated compounds has emerged. Seminal work has been reported by the Braun group in 2009, where the fluorinated pinacol boronates were synthesized from $CF_3$-substituted alkenes by the use of H–B(pin) and a catalytic amount of rhodium complex (Scheme 9).[18]

***Scheme 9***. Rh-catalyzed hydroborylation of $CF_3$-alkene




The copper(I)-catalyzed hydroborylation of $CF_3$-substituted olefins has also been reported by Yu group in 2017. They have used a β-trifluoromethyl-α,β-unsaturated ketones as a substrate with copper catalysis and $B_2(pin)_2$ to deliver the alkylboronates bearing $CF_3$ moiety. Through chiral phosphine ligand such as **L1**, the enantioenriched $CF_3$-substituted organoboron compounds were obtained in good yield (Scheme 10).[19]

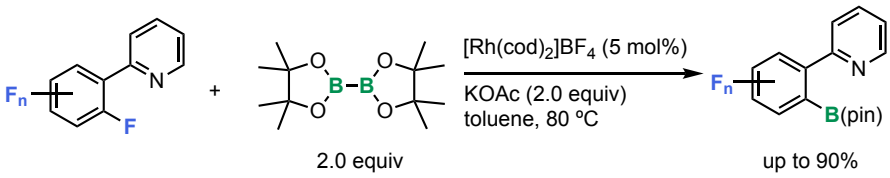
***Scheme 10***. Copper(I)-catalyzed hydroborylation of $CF_3$-bearing α,β-unsaturated ketones




The C–F activation with transition metal catalysis is another interesting strategy for the synthesis of fluorine-containing organoboron compounds.[20] In 2015, Zhang group have reported the

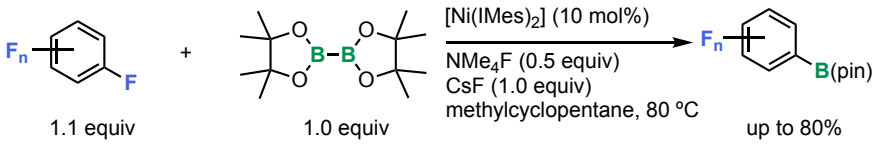
*ortho*-selective C–F bond borylation of polyfluoroarenes by the use of Rh complex as catalyst. This reaction afforded a wide range of borylated fluoroarenes that are useful for photoelectronic materials. A directing group, such as *N*-containing heteroaromatics, is necessary to control the reactivity of boryl-Rh complex toward polyfluoroarenes (Scheme 11).[21]

***Scheme 11***. Rh-catalyzed *ortho*-selective C–F borylation of polyfluoroarenes



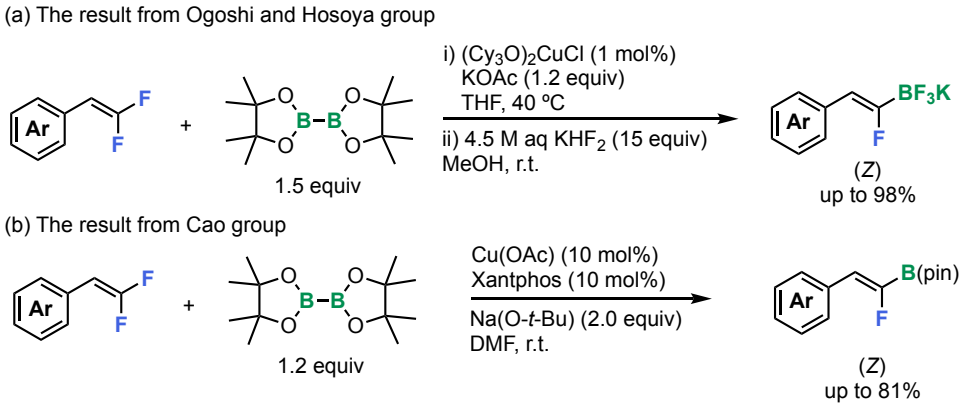

In 2016, Marder and Radius group reported an alternative method for the C–F borylation of polyfluoroarenes using $Ni(IMes)_2$ as the catalyst with $B_2(pin)_2$ as the boron source (Scheme 12).[22] They controlled the equivalent of $B_2(pin)_2$ to suppress the undesired diborylation, or triborylation of polyfluoroarens. Various partially fluorinated arenes with different degrees of fluorination were converted into monoborylated fluoroarenes, which can be conducted the typical C–C bond formation steps to allow the introduction of partially fluorinated arenes into larger organic molecules.

***Scheme 12***. Ni-catalyzed selective C–F borylation of polyfluoroarenes



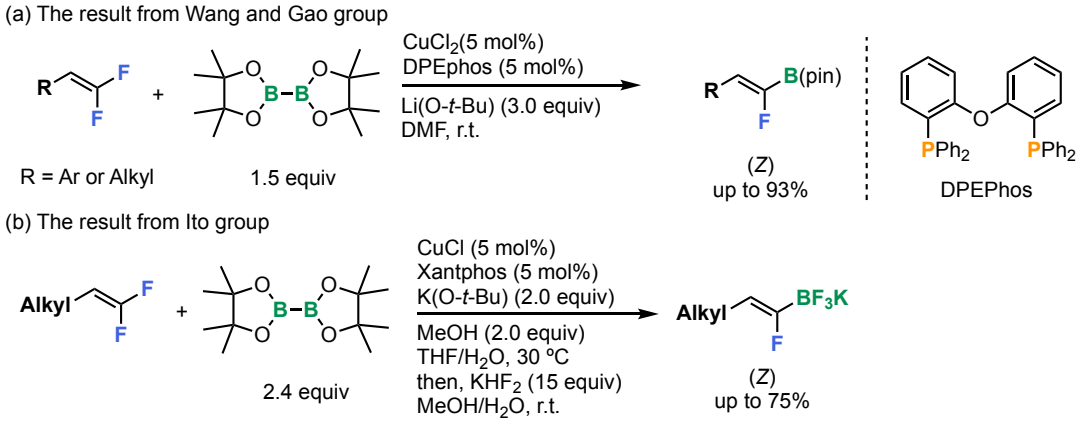

A copper-catalyzed C–F activation is also applicable for the synthesis of fluorine-containing organoboron compounds. In 2017, Ogoshi and Hosoya group reported the stereoselective defluoroborylation of aromatic *gem*-difluoroalkenes to afford the corresponding terminal monofluoroalkenes with high *Z* selectivity (Scheme 13a).[23] This reaction proceeds through insertion of a boryl-copper(I) intermediate toward *gem*-difluoro alkenes, followed by β-fluoro elimination pathways. Shortly after that report, Cao reported the similar copper(I)-catalyzed defluoroborylation reaction of *gem*-difluoro alkenes by the use of CuOAc/Xantphos catalyst system (Scheme 13b).[24]

***Scheme 13***. Copper-catalyzed defluoroborylation of aromatic *gem*-difluoroalkenes




At the almost same time, Wang and Gao group, as well as Ito group have independently reported the defluoroborylation of aromatic and aliphatic *gem*-difluoroalkenes (Scheme 14).[25,26] Wang and Gao group used the Cu(II) catalyst with DPEPhos as ligand to afford the monofluoro alkenylboronates with high *Z* selectivity. Ito group have used the Xantphos as ligand with MeOH, which somewhat suppress the generation of byproducts. Ito group isolated the compounds as the tetrafluoro borate salt due to the instability of the corresponding aliphatic monofluoro alkenyl boronates.

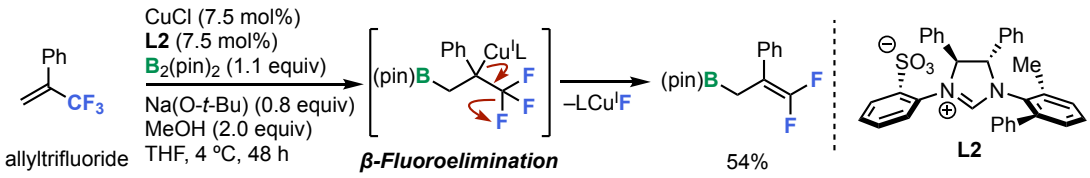
***Scheme 14***. Copper-catalyzed defluoroborylation of aliphatic *gem*-difluoroalkenes.




In 2011, Hoveyda group reported a first successful example of the copper(I) catalyzed boryl-

substitution of allyltrifluoride with NHC ligand **L2** for the synthesis of *gem*-difluoro allylboronates (Scheme 15).[27] The reaction mechanism likely proceeds via insertion of boryl-copper(I) intermediate toward the $CF_3$-alkene and the subsequent β-fluoro-elimination of the resultant copper(I)–alkyl complex to afford the product in moderate yield.

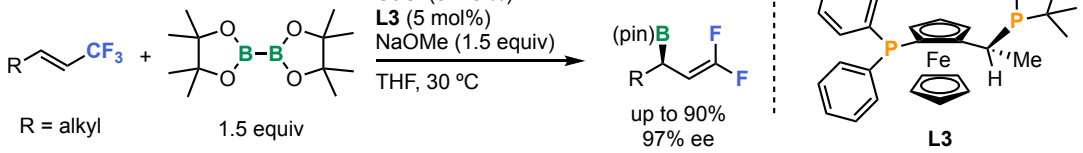
***Scheme 15***. The first example of copper(I)-catalyzed boryl-substitution of allyltrifluoride




The copper(I)-catalyzed enantioselective boryl-substitution of allyltrifluoride first reported from Ito, Shi, and Hoveyda groups independently (Scheme 16).[28–30] Ito and Shi groups have used the similar (*R*,*S*)-Josiphos type ligand **L2** and **L3** to induce high enantioselectivity (Scheme 16a, b), whereas Hoveyda group have used the chiral NHC ligand **L4** (Scheme 16c). In these reactions, a stoichiometric amount of a base was necessary, which react with the copper(I)–F intermediate generated in situ and recover copper(I) alkoxide intermediate to proceed the catalytic cycle.

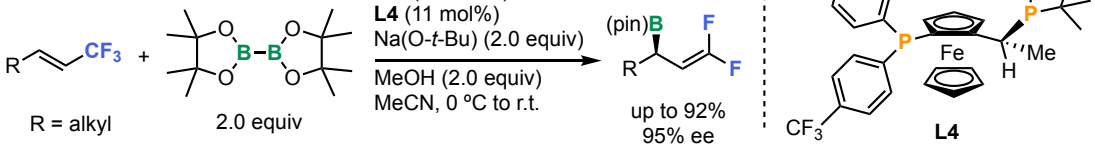
***Scheme 16***. The several examples of copper(I)-catalyzed enantioselective boryl-substitution of allyltrifluoride via β-fluoro-elimination

(a) The example from Ito group



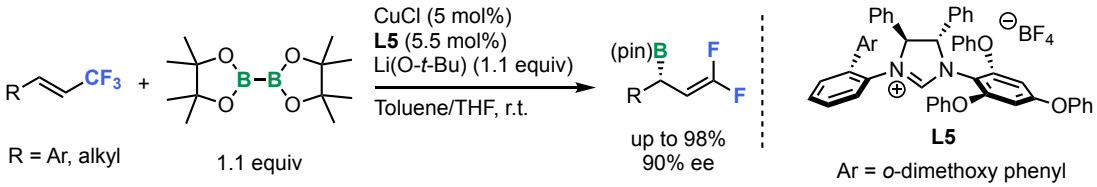

L3

(b) The example from Shi group




L4

(c) The example from Hoveyda group



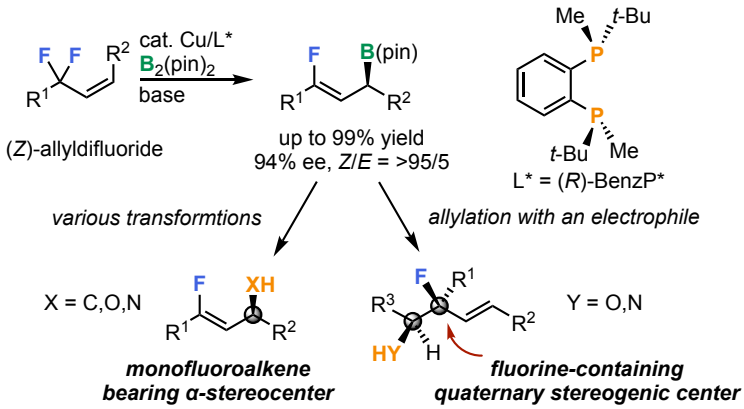

L5

Ar = *o*-dimethoxy phenyl

## 4. Overview of This Thesis

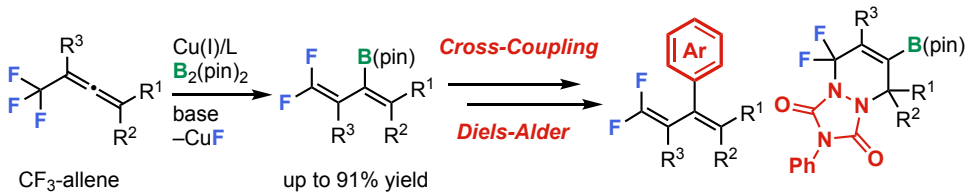
The author also focuses on the development of selective synthetic methods for several fluorine-containing organoboron compounds by means of the reactivity of boryl-copper(I) intermediate. This thesis describes new methodologies for fluorine-containing organoboron compounds and shows the utility of these compounds by the transformation toward useful fluorine-compounds.: Chapters 1, 2, and 3 describe the copper(I)-catalyzed selective borylation reaction via β-fluoro-elimination. The author previously reported that the enantioselective γ-boryl-substitution of allyltrifluode via β-fluoro-elimination with a chiral copper(I) catalyst. Guided by this success, the author hypothesized the copper(I)-catalyzed enantioselective and stereoselective γ-boryl substitution of allyldifluoride via β-fluoro-elimination would be feasible. The products in this reaction, which are (γ-monofluoro)allylboronates, would be useful fluorinated chiral building blocks because derivatization of the boryl group, as well as allylboration, would construct highly functionalized mono-fluorinated structural motifs, which include chiral monofluoroalkenes and fluorine-substituted quaternary stereogenic carbon centers (Chapter 1, Figure 6).[31]

***Figure 6***. Copper(I)-catalyzed enantio- and stereoselective γ-borylsubstitution of allyldifluoride via β-fluoroelimination




The author then extended this reaction for the $CF_3$-substituted allenes to deliver the 3-boryl-1,1-*gem*-difluorodienes. With $PPh_3$ as ligand, the products could be obtained in high yield. I proposed that the reaction proceeded via γ-selective borylcupration into the trifluoromethyl-substituted allene, followed by copper(I)-β-fluoro elimination as similar in chapter 1. The products would be good synthons for difluoro-compounds for Diels-Alder reaction or cross-coupling reaction with aryl-halides (Chapter 2, Figure 7).[32]

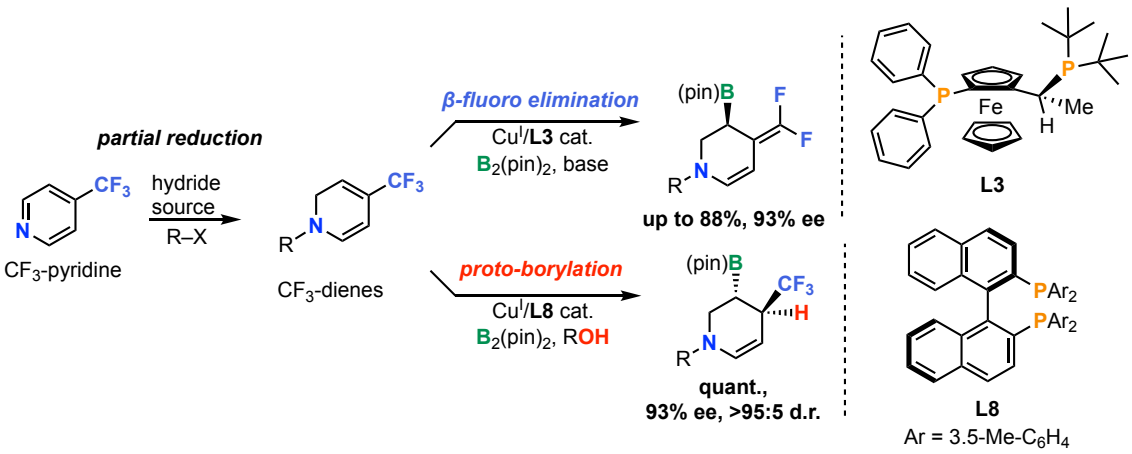
***Figure 7***. Copper(I)-catalyzed borylsubstitution of $CF_3$-allene via β-fluoroelimination




· ***The borylated products are good synthetic intermediate for difluoro-compound***

The dearomatization/enantioselective borylation sequence for the $CF_3$-pyridine afforded $CF_3$-containing chiral *N*-heterocyclic organoboronates and $CF_2$-containing chiral *N*-heterocyclic boronates separately, by choice of proper reaction conditions. The β-fluoro-elimination was occurred under the similar no-protic conditions described above, whereas the proto-borylation was occurred by the addition of alcohol as a proton source in the similar reaction. Because of the abundance of *N*-heterocyclic moieties in bioactive compounds, the versatile building blocks of fluorine-containing *N*-heterocyclic compounds would be highly attractive. This protocol offers a practical method for the synthesis of fluorine-containing heterocyclic compounds, which are key compounds for drug discovery. (Chapter 3, Figure 8).[33]

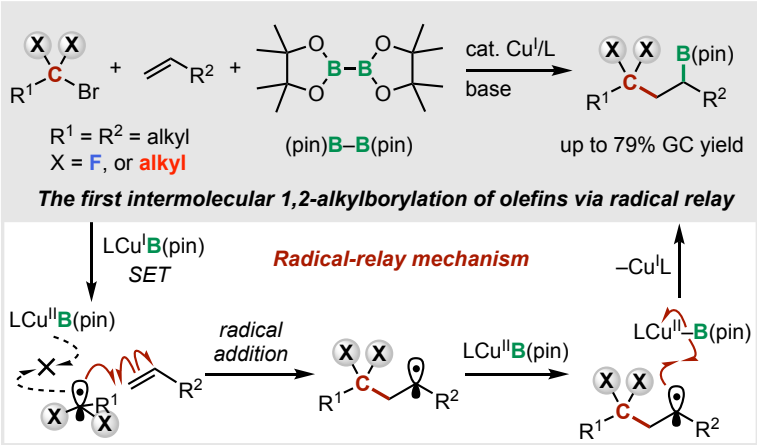
***Figure 8***. Dearomatization/enantioselective borylation sequence for the $CF_2$- and $CF_3$- containing chiral N-heterocyclic organoboronates




Chapter 4 describes a novel synthetic method for fluorine-containing compounds from non-fluorinated compounds such as terminal olefins, through a different mechanism from Chapters 1, 2, and 3. The author focuses on the use of *gem*-difluoro-alkyl bromide and tertiary-alkyl bromides with unactivated olefins with the expectation that the low reactivity of the radical intermediates generated by these electrophiles would not undergo the boryl-substitution reaction under the borylation reaction conditions with copper(I) catalysis. The reaction with those

electrophiles and olefins proceeded via radical-relay mechanism to afford the γ,γ-*gem*-difluoro alkylboronates, and γ-tertiary alkylboronates. This is the first example of the intermolecular 1,2-alkylborylation of olefins via radical-relay mechanism (Chapter 4, Figure 9).[34]

***Figure 9***. Copper(I)-catalyzed intermolecular 1,2-alkylborylation of unactivated olefins via radical-relay mechanism




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# Chapter1

# Copper(I)-Catalyzed γ-Boryl Substitution of Allyldifluoride via β-Fluoroelimination

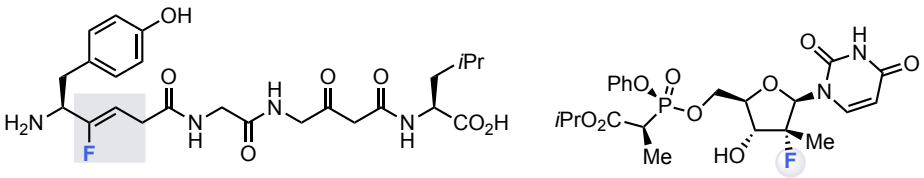
## Abstract

A new method has been developed for the catalytic enantio- and stereoselective synthesis of (*Z*)-(γ-monofluoroallyl)boronates via the copper(I)-catalyzed γ-boryl substitution of allyl difluorides. Subsequent transformations of the boryl group in the (*Z*)-(γ-monofluoroallyl)boronates provided the various functionalized chiral monofluoroalkenes in a highly stereospecific manner. The utility of the (*Z*)-(γ-monofluoroallyl)boronates was further demonstrated by allylation of aldehydes and aldimines to form fluorine-substituted quaternary stereogenic carbon center with high stereoselectivity and stereospecificity.


## Introduction

As I mentioned, new methods for the synthesis of organofluorine compounds have been targeted in recent years due to the differences in the physical and biological properties between fluorinated analogues and those of their nonfluorinated compounds.[1] In this context, fluorine-containing optically active compounds have attracted increasing attention because of their valuable applications in pharmaceutical, agrochemical, and material industries.[1] Among those compounds, the enantioenriched monofluorinated compounds are of great interest in the past decades (Figure 1).[2]

***Figure 1***. The example of bioactive compounds bearing monofluoro moieties.

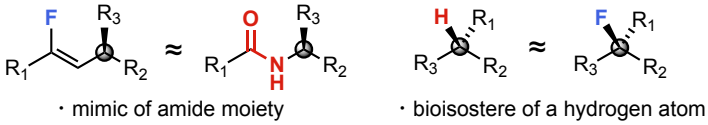



Fluoro-substituted Leu-enkephalin

Sofosbuvir

For example, monofluoroalkenes bearing an α-stereocenter are considered to be ideal mimics for peptide bond analogues due to their steric and electronic similarities (Figure 2).[3] Additionally, organic compounds bearing fluorine-substituted quaternary stereogenic carbon centers have attracted significant interests because they are isosteric with common stereogenic carbon centers bearing a single hydrogen atom.[4] Despite recent progress in the synthesis of organofluorine compounds, however, stereo- and enantioselective syntheses of this class of chiral compounds remain challenging. Especially, the development of efficient methods for construction of chiral fluorine-substituted quaternary stereogenic carbon center has been elusive.[5,6] Therefore, the development of useful building blocks for accessing these chiral monofluorinated molecules would give a great impact on synthetic chemistry and drug discovery.

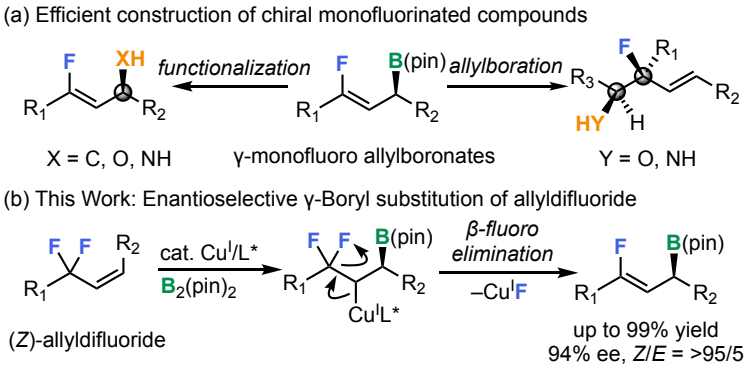
***Figure 2.*** Monofluoro moieties become several bioisostere




Fluorine-containing organoboron compounds are undoubtedly attractive synthetic synthons which have great potential for the flexible assembly of an array of structurally diverse organofluorine compounds.[7] Among such compounds, (γ-monofluoro)allylboronates would become one of the most useful fluorinated chiral building blocks because derivatization of the boryl group such as allylboration would construct highly functionalized mono-fluorinated structural motifs, which include chiral monofluoroalkenes and fluorine-substituted quaternary stereogenic carbon centers (Scheme 1a). However, there is no report of the stereo- and enantioselective synthesis of (γ-monofluoroallyl)boronates to date.

Recently, transition-metal-mediated C–F bond activation has emerged to be a powerful methodology for the synthesis of fluorinated molecules.[1c,8-10] My group and Shi have independently reported the catalytic enantioselective γ-boryl substitution of $CF_3$-substituted alkenes to give optically active *gem*-difluoroallylboronates in high yields with excellent enantioselectivities using a chiral copper(I) catalyst.[9,10c] This reaction presumably proceeds through the enantioselective borylcupration of alkenes, followed by the copper(I)-*β*-fluoro elimination.[9,10] In this work, the author report the first enantioselective synthesis of enantioenriched (*Z*)-(γ-monofluoro)allylboronates via the chiral bisphosphine/copper(I) complex-catalyzed γ-boryl substitution of allyldifluorides through *β*-fluoroelimination, where simultaneous control of stereoselectivity and enantioselectivity is required (Scheme 1b). Derivatizations of the products using boryl groups, such as oxidation, homologation, and amination provided the corresponding chiral functionalized monofluoroalkenes in a stereospecific manner. Notably, allylboration of aldehydes and aldimines with (*Z*)-(γ-monofluoro)allylboronates allowed to construct fluorine-substituted quaternary stereogenic carbon center with excellent enantiomeric purity.

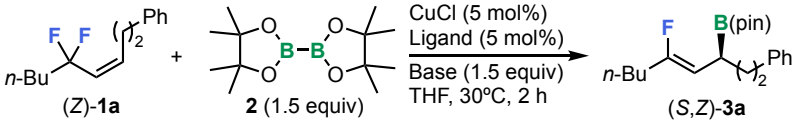
***Scheme 1.*** The summary of this work




## Result and Discussion

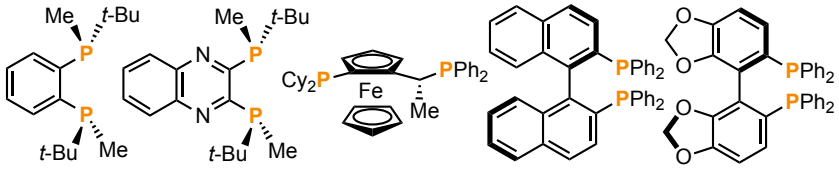
The results of an extensive optimization study revealed that the reaction of (*Z*)-(5,5-difluoronon-3-en-1-yl)benzene (**1a**) with bis(pinacolato)diboron (**2**) in the presence of CuCl/(*R*,*R*)-BenzP* (5 mol%), NaOMe (1.5 equiv) in THF at 30°C afforded the (γ-monofluoro)allylboronate (*S*,*Z*)-**3a** in high yield with excellent *Z*/*E* ratio, and enantioselectivity (99% yield, *Z*/*E* = 95/5, 94% ee; Table 1, entry 1). The use of (*R*,*R*)-QuinoxP* also provided high levels of enantioselectivity (93% yield, *Z*/*E* = 95/5, 92% ee; Table 1, entries 2). However, the use of other chiral phosphine ligands such as (*R*,*S*)-Josiphos, (*R*)-BINAP, and (*R*)-Segphos led to a significant decrease in reactivity and enantioselectivity (Table 1, entries 3–5). The nature of the used base was also determined to have an important effect on reactivity and enantioselectivity (Table 1, entries 6–8). For example, the use of KOMe as base resulted in a slight decrease in reactivity and enantioselectivity, but the use of other bases such as LiOMe or Na(O-*t*-Bu) led to significant decrease in reactivity. These results indicated that the sodium counter cation is crucial for this reaction rather than potassium or lithium counter cation of the base. Upon decreasing the amount of NaOMe to 10 mol%, the boryl substitution scarcely proceeded (Table 1, entry 9). Lower reaction temperature resulted in a slight decrease of enantioselectivity (97% yield, *Z*/*E* = 97:3, 93% ee; Table 1, entry 10). Finally, when toluene was used as the solvent, the reaction rate was decreased (70% yield, *Z*/*E* = 94:6, 92% ee; Table 1, entry 11).

***Table 1.*** Optimization of the reaction conditions[a]




| Entry | Ligand | Base | Yield (%)[b] | *E*/*Z*[c] | Ee (%)[d] |
|---|---|---|---|---|---|
| 1[e] | (*R*,*R*)-BenzP* | NaOMe | 99(93) | 95/5 | 94 |
| 2 | (*R*,*R*)-QuinoxP* | NaOMe | 93 | 95/5 | 92 |

| | | | | | |
|---|---|---|---|---|---|
| 3 | (*R*,*S*)-Josiphos | NaOMe | 66 | 93/8 | 66 |
| 4 | (*R*)-BINAP | NaOMe | trace | – | – |
| 5 | (*R*)-Segphos | NaOMe | 36 | 91/9 | 0 |
| 6 | (*R*,*R*)-BenzP* | KOMe | 85 | 96/4 | 90 |
| 7 | (*R*,*R*)-BenzP* | LiOMe | trace | – | – |
| 8 | (*R*,*R*)-BenzP* | Na(O-*t*-Bu) | 16 | – | – |
| 9[f] | (*R*,*R*)-BenzP* | NaOMe | trace | – | – |
| 10[g] | (*R*,*R*)-BenzP* | NaOMe | 97 | 97/3 | 93 |
| 11[h] | (*R*,*R*)-BenzP* | NaOMe | 70 | 94/6 | 92 |



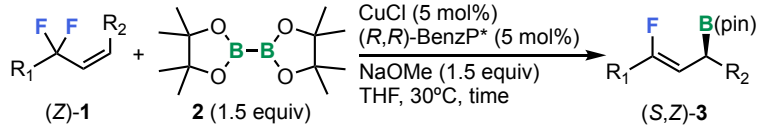

(*R*,*R*)-BenzP* (*R*,*R*)-QuinoxP* (*R*,*S*)-Josiphos (*R*)-BINAP (*R*)-Segphos

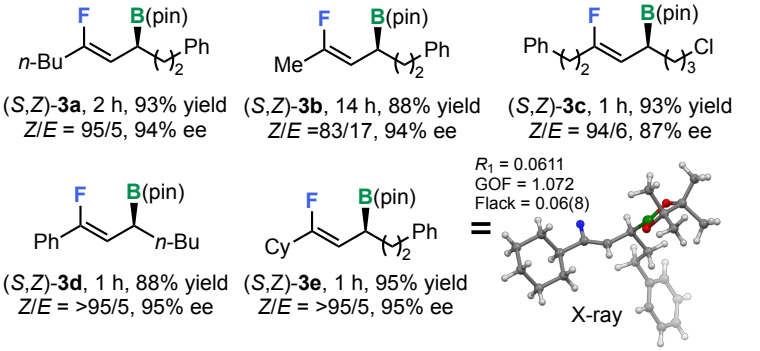
[a]Conditions: **1a** (0.20 mmol), CuCl (0.010 mmol), ligand (0.010 mmol), base (0.30 mmol), 2 (0.30 mmol) in THF (400 μL). [b]Determined by $^{19}$F NMR analysis of crude mixture with an internal standard. [c]*E*/*Z* ratio was determined by GC analysis. [d]The ee values of the products were determined by HPLC analysis of the saturated alcohols derived from the corresponding boronates. [e]*0.5 mmol scale.* Isolated yield is shown in parentheses. [f]10 mol% NaOMe was used as base. [g]The reaction was conducted at 0°C. [h]Toluene was used as solvent.

Next, the optimized conditions were used for further evaluation of the substrate scope (Table 2). Substrates containing a methyl, chloride or phenyl group [(*Z*)-**1b-1d**] afforded the products in high yield with excellent *Z*/*E* ratios, and enantioselectivities [(*S*,*Z*)-**3b**: 88% yield, *Z*/*E* = 83/17, 94% ee; (*S*,*Z*)-**3c**: 93% yield, *Z*/*E* = 94/6, 87% ee; (*S*,*Z*)-**3d**: 88% yield, *Z*/*E* =>95/5, 95% ee]. The (γ-monofluoro)allylboronate bearing a cyclohexyl group (*S*,*Z*)-**3e**, was also formed in 88% yield with *Z*/*E* = >95/5 and 95% ee. X-ray crystallography analysis of boronate (*S*,*Z*)-**3e** was conducted to determine absolute configuration. The allyl difluorides bearing acetoxy, benzyl ether and silyl ether groups [(*Z*)-**1f**–**1h**] also reacted smoothly to give the corresponding products in high yields with excellent stereoselectivities [(*S*,*Z*)-**1f**, 90% yield, *Z*/*E* = 90/10, 92% ee; (*S*,*Z*)-**1g**, *Z*/*E* = 94/6, 92% ee; (*S*,*Z*)-**1h**, *Z*/*E* =95/5, 92% ee]. The use of nitrogen-containing substrate (*Z*)-**1i** provided the corresponding product (*S*,*Z*)-**3i** with excellent *Z*/*E* ratio and enantioselectivity, while the yield was slightly decreased because of the instability of the product toward silicagel-column chromatography [(*S*,*Z*)-**3i,** 56% yield, *Z*/*E* =95/5, 90% ee]. The application of the optimized conditions to the α-trimethylsillyl allyldifluoride [(*Z*)-**1j**] led to an excellent *Z*/*E* ratio, but the reactivity and enantioselectivity were only moderate [(*S*,*Z*)-**3j**, 30% yield, *Z*/*E* = 95/5,

77% ee]. The reaction of the difluoro-substituted terminal alkene **1k** afforded corresponding product **3k**, while the *E*/*Z* ratio was drastically decreased (95% yield, *Z*/*E* = 50/50, 87% ee).

***Table 2.*** Optimization of the reaction conditions[a]

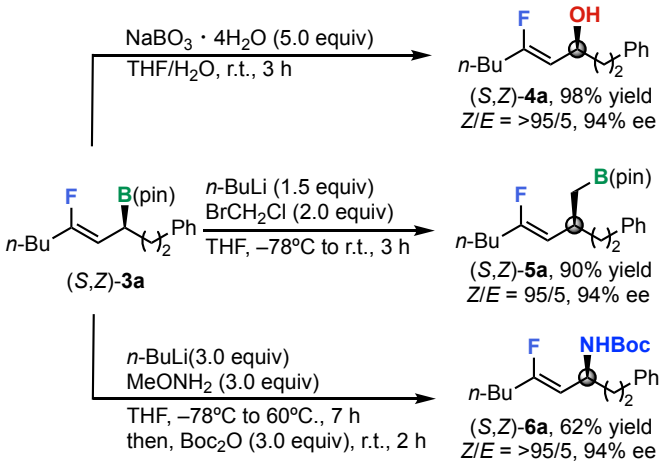



[a]Conditions: (*Z*)-**1** (0.50 mmol), CuCl (0.025 mmol, (*R*,*R*)-BenzP* (0.025 mmol), NaOMe (0.75 mmol), **2** (0.75 mmol) in THF (1.0 mL) at 30ºC. Yields of isolated products are reported. The ee values of the products were determined by HPLC analysis of the saturated alcohols or corresponding ester derived from the corresponding boronates. *E*/*Z* ratio was determined by GC analysis.

To demonstrate the utility of these enantioenriched fluorinated allylboronates, I conducted several stereospecific transformations by using the boron moiety for the synthesis of chiral functionalized monofluoroalkenes (Scheme 2). The fluorine-containing boronate (*S*,*Z*)-**3a** was subjected to $NaBO_3$ oxidation, homologation with a halomethyl lithium reagent, or amination with methoxyamine.[11-13] These reactions afforded the corresponding alcohol (*S*,*Z*)-**4a**, alkyl boronate (*S*,*Z*)-**5a**, and Boc-protected amine (*S*,*Z*)-**6a** with excellent stereospecificity. These results therefore suggested that the borylation products will provide attractive synthetic pathways for the stereocontrolled synthesis of α-chiral monofluorinated alkene derivatives**.**

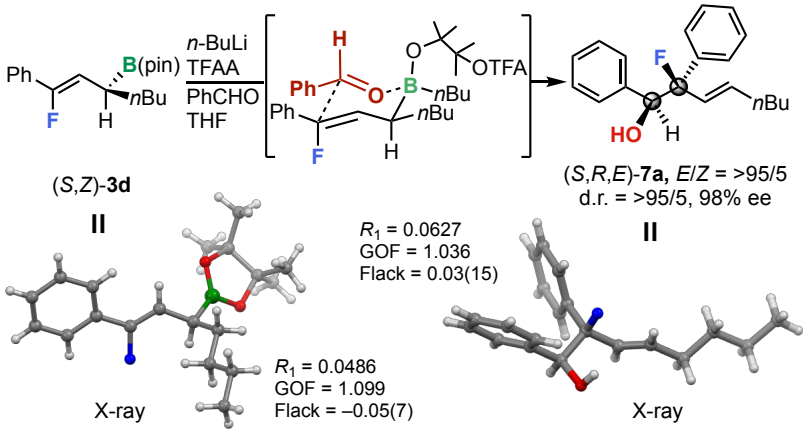
***Scheme 2.*** Transformations of (γ-monofluoroallyl)boronate for the Synthesis of functionalized chiral monofluoroalkenes.




[a]Conditions: **3** (0.10 mmol), ArBr (0.15 mmol), $Pd(OAc)_2$ (0.005 mmol), SPhos (0.010 mmol), and 2.5M $NaOH_{aq}$ (0.30 mmol) in THF (210 μL). [b]ArBr (1.05 equiv) was used. [c]Determined by GC analysis.

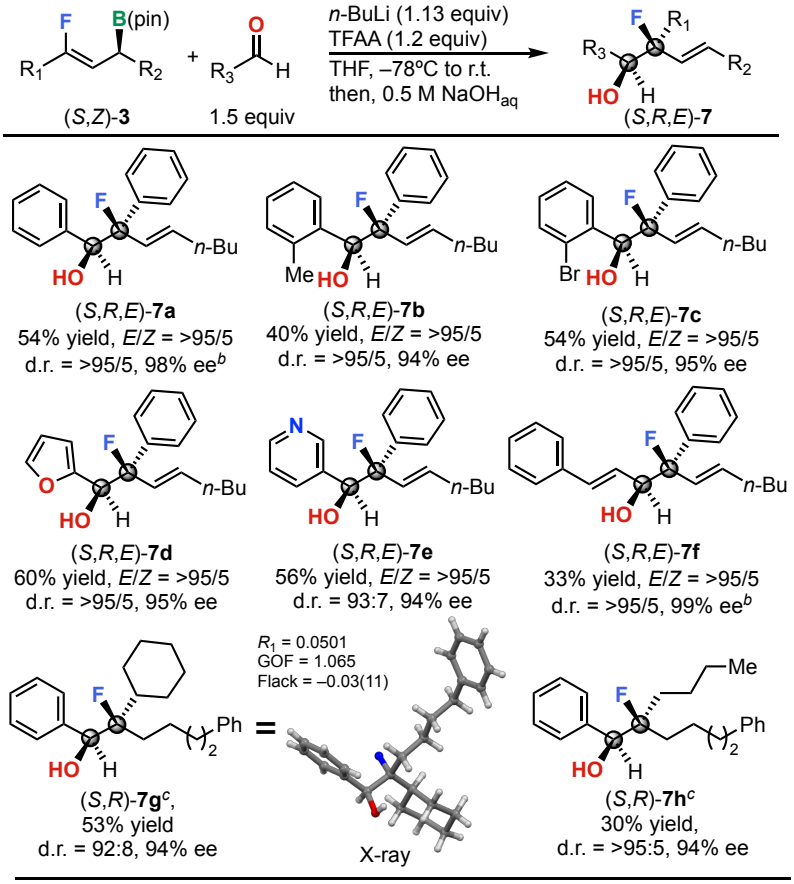
Next, the author focused on allylation reactions with (γ-monofluoroallyl)boronates (*S*,*Z*)-**3** for the construction of fluorine-substituted quaternary stereogenic carbon center that are otherwise challenging to construct (Scheme 3). The reaction of (*S*,*Z*)-**3d** with benzaldehyde using Aggarwal's allylation conditions after basic work-up afforded the corresponding fluorohydrin bearing fluorine-substituted quaternary stereogenic center in high stereoselectivity and stereospecificity [(*S*,*R*,*E*)-**7a**].[14,15] The absolute stereochemistry of the borylation product (*S*,*Z*)-**3d** and allylation product [(*S*,*R*,*E*)-**7a**] were determined by X-ray crystallographic analysis (Scheme 3).

***Scheme 3.*** Allylation reactions for the construction of fluorine-substituted stereogenic carbon center.




Several other enantioenriched fluorohydrins were also obtained by this allylation reactions (Table 3). The reaction of (*S*,*Z*)-**3d** with 2-methylbenzealdehyde and 2-bromobenzaldehyde afforded the corresponding products in high stereoselectivities and stereospecificities [(*S*,*R*,*E*)-**7b** and (*S*,*R*,*E*)-**7c**]. Other aldehydes that bear furan and pyridine bearing aldehydes as well as 1,2-conjugated aldehyde also reacted with (*S*,*Z*)-**3d** to give the corresponding chiral fluorohydrins [(*S*,*R*,*E*)-**7d**–**7f**]. Additionally, the reaction of (*S*,*Z*)-**3e** and (*S*,*Z*)-**3a** with benzaldehyde, followed by the Pd/C hydrogenation reaction provided fluorohydrine (*S*,*E*)-**7g** and (*S*,*E*)-**7h**, respectively.[16]

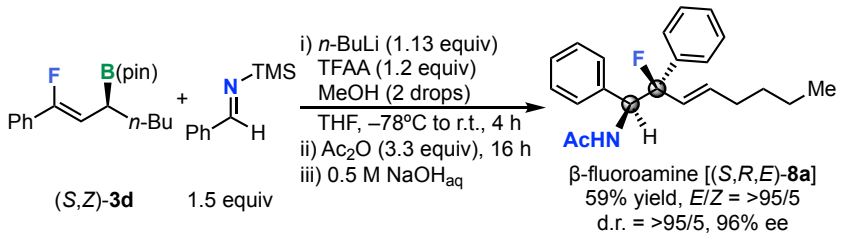
**Table 3.** Scope of the allylation for the synthesis of enantioenriched fluorohydrins bearing fluorine-substituted stereogenic carbon center.




[a]Conditions: (*S*,*Z*)-**3** (0.10 mmol), *n*-BuLi (0.113 mmol), TFAA (0.12 mmol), aldehyde (0.15 mmol), in THF (1.0 mL); T = –78°C to r.t. Yields of isolated products are reported. The *E*/*Z* ratio of the products was determined by $^1$H NMR analysis. The ee values of the products were determined by HPLC. [b]The product was isolated by hexane wash for the solid of crude material. For this reason, the ee value of the product was increased compared to the borylated product. [c]The product was isolated after hydrogenation with 10% Pd/C in MeOH.

Chiral *β*-fluoroamines are of great importance in medicinal chemistry because a *β*-fluoro substituent lowers the *p*K$_a$ value of the neighboring amines and can thus improve pharmacological properties in some cases.[17] I conducted the allylation of *N*-trimethylsilyl benzaldiimine with (*S*,*E*)-**3d** (Scheme 4). As a result, the chiral secondary amine bearing a fluorine-substituted quaternary stereogenic center (*S*,*R*,*E*)-**8a** was obtained with high stereoselectivity and stereospecificity.

**Scheme 4. Allylation of *N*-TMS-aldimine for the synthesis of *β*-fluoroamine.**




## Conclusion

In summary, the author developed a stereo- and enantioselective copper(I)-catalyzed γ-boryl substitution of difluoro-substituted alkenes that provides access to optically active (*Z*)-(γ-monofluoroallyl)boronates. The borylated products of this reaction could be stereospecifically converted into chiral monofluoroalkene derivatives through boron functionalization processes. Importantly, the fluorine-substituted quaternary stereogenic carbon centers were formed via stereoselective allylation reactions of aldehydes and aldimines with the (γ-monofluoroallyl)boron reagents. I therefore believe that the newly synthesized organoboron reagents, (*Z*)-(γ-monofluoroallyl)boronates, will be useful chiral building blocks for the preparation of various chiral organofluorine compounds, which are difficult to access by any other method.

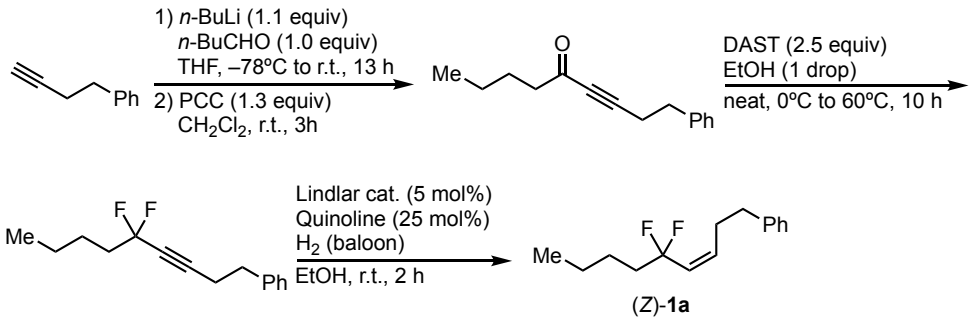
# Experiment

## 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 ($^{1}$H: 392, 396, 399, 400 and 401 MHz, $^{13}$C: 100 MHz and $^{19}$F: 373 MHz). Tetramethylsilane ($^{1}$H), $CDCl_3$ ($^{13}$C) and Fluorobenzene ($^{19}$F, δ –113.60) were employed as the external standards, respectively. Fluorobenzene 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, m = multiplet. CuCl (ReagentPlus® grade, 224332-25G, ≥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.

## Substrate Preparation Procedures

**Preparation of (*Z*)-(5,5-difluoronon-3-en-1-yl)benzene [(*Z*)-1a].[18]**




In a vacuum dried 200 mL round bottomed flask, *n*-BuLi (1.6 M hexane solution, 20.6 mL) was added dropwise to the mixture of 3-butyn-1-ylbenzene (4.6 mL, 33 mmol) and dry THF (45 mL) at –78 ºC under a nitrogen atmosphere. After 30 minutes, *n*-BuCHO (3.2 mL, 30 mL) was added dropwise to the reaction mixture, then warmed up to room temperature and stirred for 13 hours. The reaction mixture was quenched by aqueous $NH_4Cl$ solution at 0ºC and 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) to give the corresponding alcohol (5.08 g, 78% yield) as a colorless oil.

In a vacuum dried 200 mL round bottomed flask, pyridinium chlorochromate (PCC) (6.3 g, 29.3 mmol) was dissolved in $CH_2Cl_2$ (47 mL) and cooling to 0 ºC. The alcohol (5.08 g, 23.4 mmol) in $CH_2Cl_2$ (23.4 mL) was added dropwise to this flask over 10 minutes. After the mixture was stirred for 12 hours at room temperature, $Et_2O$ (50 mL) was added and the reaction mixture was filtered through a Celite pad and concentrated under reduced pressure. The crude product was purified by flash column chromatography ($SiO_2$, EtOAc/Hexane 0:100–15:85) to give the corresponding ketone (3.23 g, 65% yield) as a colorless oil.

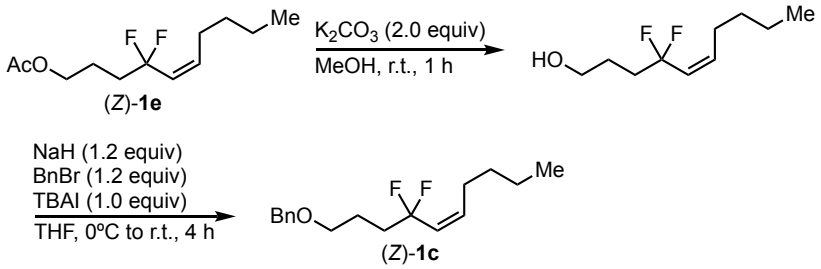
In a vacuum dried 50 mL round bottomed flask, *N*,*N*-dimethylaminosulfur trifluoride (DAST) (4.9 mL, 37.5 mmol) was added by one portion to the corresponding ketone (3.23 g, 15.0 mmol) at 0 ºC. EtOH (1 drop) was added and the mixture was stirred for 12 h at 60 ºC. $CH_2Cl_2$ (20 mL) was then added and the reaction mixture was quenched by aqueous $NH_4Cl$ at 0 ºC and extracted with $CH_2Cl_2$. The crude product was purified by flash column chromatography ($SiO_2$, Hexane only) to give the corresponding difluoro compound (1.78 g, 50% yield) as a brown oil.

In a vacuum dried 50 mL round bottomed flask, Lindlar catalyst (744.9 mg, 0.35 mmol) was dissolved in EtOH (100 mL) and quinoline (207 μL, 1.75 mmol) was added to this mixture. The corresponding difluoro compound (1.78 g, 7.0 mmol) was then added to this mixture and stirred for 2 h under $H_2$ atomosphere ($H_2$ baloon). The reaction mixture was then filtered through a Celite pad and

concentrated under reduced pressure. The crude product was purified by flash column chromatography ($SiO_2$, Hexane only). (*Z*)-**1a** was obtained in 73% yield (1.56 g, 6.6 mmol) as a colorless oil.

$^1$H NMR (396 MHz, $CDCl_3$, δ): 0.90 (t, *J* = 7.1 Hz, 3H), 1.25–1.44 (m, 4H), 1.74–1.89 (m, 2H), 2.53–2.62 (m, 2H), 2.70 (t, *J* = 7.5 Hz, 2H), 5.40–5.53 (m, 1H), 5.70 (tdt, *J* = 1.9, 7.7, 11.7 Hz, 1H), 7.18–7.31 (m, 5H). $^{13}$C NMR (100 MHz, $CDCl_3$, δ): 13.8 (*C*$H_3$), 22.4 (*C*$H_2$), 24.4 (*C*$H_2$), 30.1 (*C*$H_2$), 35.6 (*C*$H_2$), 38.1 (t, *J* = 26.8 Hz, *C*$H_2$), 122.7 (t, *J* = 241.4 Hz, *C*), 125.4 (t, *J* = 27.8 Hz, *C*H), 126.0 (*C*H), 128.4 (d, *J* = 10.6 Hz, *C*H), 136.4 (t, *J* = 6.2 Hz, *C*H), 141.3 (*C*). $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –91.3 (d, *J* = 34.3 Hz, 2F). HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{15}H_{20}F_2$, 238.1533; found, 238.1532.

**Preparation of (*Z*)-{[(4,4-difluorodec-5-en-1-yl)oxy]methyl}benzene [(*Z*)-1c].**

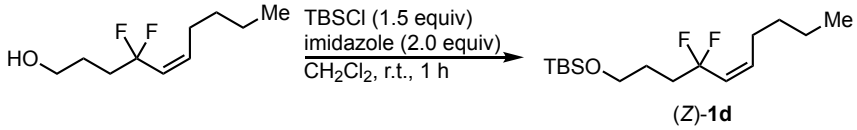



(*Z*)-**1e** was added to a solution of $K_2CO_3$ (2.21 g, 16 mmol) in MeOH (100 mL). After stirring for 1 h, the solution was filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography ($SiO_2$, Hexane only) to afford the corresponding alcohol in 89% yield (1.37 g, 7.1 mmol) as a colorless oil.

The corresponding alcohol (384.5 mg, 2.0 mmol) was added dropwise to a solution of NaH (95.2 mg, 2.4 mmol) in THF (5.0 mL) at 0 ºC. BnBr (282 μL, 2.38 mmol) was then added dropwise and the reaction mixture was stirred at room temperature for 4 h. The mixture was quenched by $H_2O$ and extracted with $Et_2O$. The crude product was purified by flash column chromatography ($SiO_2$, Hexane only) to afford (*Z*)-**1c** in 75% yield (421.3 mg, 1.5 mmol) as a colorless oil.

$^1$H NMR (392 MHz, $CDCl_3$, δ): 0.90 (t, *J* = 7.3 Hz, 3H), 1.24–1.44 (m, 4H), 1.74–1.86 (m, 2H), 1.93–2.11 (m, 2H), 2.20–2.29 (m, 2H), 3.52 (t, *J* = 6.3 Hz, 2H), 4.51 (s, 2H), 5.38–5.52 (m, 1H), 5.65–5.76 (m, 1H), 7.23–7.38 (m, 5H). $^{13}$C NMR (100 MHz, $CDCl_3$, δ): 13.8 (*C*$H_3$), 22.2 (*C*$H_2$), 22.8 (*C*$H_2$), 27.9 (*C*$H_2$), 31.4 (*C*$H_2$), 35.3 (t, *J* = 27.2 Hz, *C*$H_2$), 69.3 (*C*$H_2$), 72.7 (*C*$H_2$), 122.5 (t, *J* = 238.4 Hz, *C*), 124.5 (t, *J* = 27.2 Hz, *C*H), 127.4 (*C*H), 128.2 (*C*H), 138.0 (t, *J* = 6.2 Hz, *C*H), 138.3 (*C*). $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –91.4 (d, *J* = 34.3 Hz, 2F). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{17}H_{24}OF_2Na$, 305.1687; found, 305.1688.

**Preparation of (*Z*)-*tert*-butyl[(4,4-difluorodec-5-en-1-yl)oxy]dimethylsilane [(*Z*)-1d].**

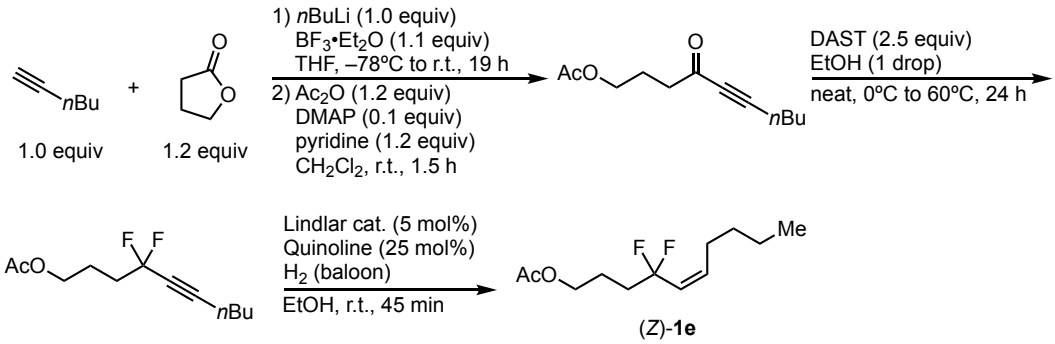



(*Z*)-**1d**

The corresponding alcohol (384.5 mg, 2.0 mmol) was added dropwise to a solution of imidazole (272.3 mg, 4.0 mmol) in $CH_2Cl_2$ (5.0 mL) at room temperature. TBSCl (452.2 mg, 3.0 mmol) was then added to the solution and the reaction mixture was stirred at room temperature for 1 h. The mixture was quenched by $H_2O$ and extracted with $Et_2O$. The crude product was purified by flash column chromatography ($SiO_2$, Hexane only) to afford (*Z*)-**1d** in 58% yield (355.1 mg, 1.2 mmol) as a colorless oil.

$^1$H NMR (401 MHz, $CDCl_3$, δ): 0.05 (s, 6H), 0.89–0.92 (m, 12H), 1.28–1.42 (m, 4H), 1.64–1.73 (m, 2H), 1.92–2.05 (m, 2H), 2.21–2.29 (m, 2H), 3.65 (t, *J* = 6.4 Hz, 2H), 5.40–5.51 (m, 1H), 5.71 (tdt, *J* = 1.8, 7.8, 11.7 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$, δ): –5.4 (*C*H$_3$), 13.9 (*C*H), 18.2 (*C*), 22.3 (*C*H$_2$), 25.8 (*C*H$_2$), 25.9 (*C*H$_3$), 28.1 (*C*H$_2$), 31.6 (*C*H$_2$), 35.1 (t, *J* = 27.3 Hz, *C*H), 62.3 (*C*H$_2$), 122.7 (t, *J* = 236.4 Hz, *C*), 124.8 (t, *J* = 27.2 Hz, *C*H), 138.0 (t, *J* = 5.8 Hz, *C*H). $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –91.1 (s, 2F). HRMS–EI (*m*/*z*): $[M+Na]^+$ calcd for $C_{16}H_{32}OF_2NaSi$, 329.2083; found, 329.2085.

**Preparation of (*Z*)-4,4-difluorodec-5-en-1-yl acetate [(*Z*)-1e].[18]**




(*Z*)-**1e**

In a vacuum dried 500 mL round bottomed flask, *n*-BuLi (1.6 M in hexane, 37.5 mL) was added dropwise to the mixture of hex-1-yne (6.9 mL, 60 mmol) and dry THF (180 mL) at –78 ºC under a nitrogen atmosphere. After 30 minutes, $BF_3$•$Et_2O$ (66 mL) was added dropwise to the reaction mixture. The reaction mixture was then stirred for 30 minutes, and dihydrofuran-2(3*H*)-one was added dropwise to the reaction mixture. The reaction mixture was warmed up to room temperature over the course of 19 h. The reaction mixture was then quenched by aqueous $NH_4Cl$ at 0 ºC and 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) to give the corresponding γ-hydroxy ketone (5.47 g, 54% yield) as a colorless oil.

In a vacuum dried 200 mL round bottomed flask, the γ-hydroxy ketone (30 mmol) was dissolved

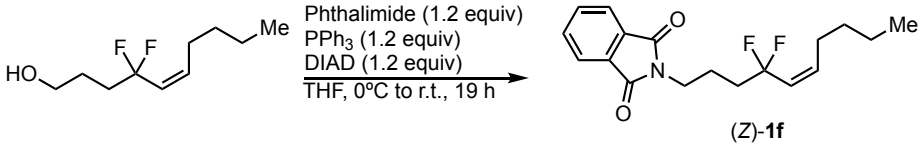
in $CH_2Cl_2$ (90 mL). To this solution, DMAP (367.0 mg, 3.0 mmol), pyridine (2.91 mL, 36 mmol) and $Ac_2O$ (3.4 mL, 36 mmol) was added at room temperature. After the mixture was stirred for 17 hours, the mixture was quenched by $H_2O$ and extracted with $CH_2Cl_2$. After the removal of the solvent, the crude product was purified by flash column chromatography ($SiO_2$, EtOAc/Hexane 0:100–15:85) to give the corresponding ketone (6.97g, quant.) as a colorless oil.

In a vacuum dried 100 mL round bottomed flask, DAST (9.9 mL, 75.0 mmol) was added by one portion to the corresponding ketone (6.97 g, 30 mmol) at 0 ºC. EtOH (1 drop) was added and the mixture was stirred for 22 h at 60 ºC. $CH_2Cl_2$ (40 mL) was added then and the reaction mixture was carefully quenched by aqueous $NH_4Cl$ at 0 ºC and extracted with $CH_2Cl_2$. The crude product was purified by flash column chromatography ($SiO_2$, EtOAc/Hexane 0:100–7:93) to give the corresponding difluoro compound (3.03 g, 44% yield) as a brown oil.

In a vacuum dried 300 mL round bottomed flask, Lindlar catalyst (1.19 g, 0.56 mmol) was dissolved in EtOH (200 mL) and quinoline (331 μL, 2.8 mmol) was added to this mixture. Then, the difluoro compound (2.73 g, 11.2 mmol) was added to this mixture and stirred for 45 minutes under $H_2$ atmosphere ($H_2$ baloon). The reaction mixture was then filtered through a Celite pad and concentrated under reduced pressure. The crude product was purified by flash column chromatography ($SiO_2$, Hexane only) to give (*Z*)-**1e** in 86% yield (2.36 g, 9.63 mmol) as a colorless oil.

$^1$H NMR (392 MHz, $CDCl_3$, δ): 0.91 (t, *J* = 7.1 Hz, 3H), 1.28–1.43 (m, 4H), 1.79–2.05 (m, 4H), 2.06 (s, 3H), 2.20–2.29 (m, 2H), 4.10 (t, *J* = 6.5 Hz, 2 H), 5.45 (tdt, *J* = 1.7, 12.2, 14.1 Hz, 1H), 5.73 (tdt, *J* = 1.9, 7.8, 11.7 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$, δ): 13.6 (*C*$H_3$), 20.6 (*C*$H_3$), 21.7 (t, *J* = 4.3 Hz, *C*$H_2$), 22.1 (*C*$H_2$), 27.8 (*C*$H_2$), 31.4 (*C*$H_2$), 34.9 (t, *J* = 27.3 Hz, *C*$H_2$), 122.0 (t, *J* = 240.5 Hz, *C*), 124.2 (t, *J* = 27.3 Hz, *C*H), 138.3 (*C*H), 170.7 (*C*). $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –91.6 (d, *J* = 34.3 Hz, 2F). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{12}H_{20}O_2F_2Na$, 257.1324; found, 257.1326.

**Preparation of (*Z*)-2-(4,4-difluorodec-5-en-1-yl)isoindoline-1,3-dione [(*Z*)-1f].**



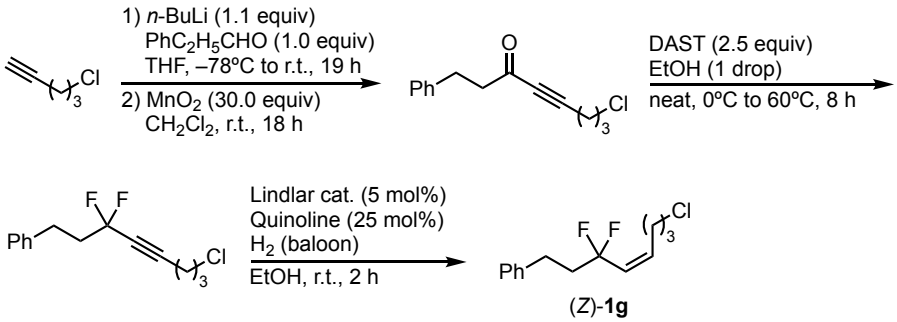

(*Z*)-**1f**

DIAD (467 μL, 2.4 mmol) was added dropwise to a solution of phthalimide (353.1 mg, 2.4 mmol), $PPh_3$ (629.5 mg, 2.4 mmol) and the corresponding alcohol (384.5 mg, 2.0 mmol) in THF (5.0 mL) at 0 ºC. The reaction mixture was stirred at room temperature for 19 h. and then concentrated under reduced pressure. The crude product was purified by flash column chromatography ($SiO_2$, EtOAc/Hexane 4:96–10:90) to afford (*Z*)-**1f** in 70% yield (451.7 mg, 1.4 mmol) as a colorless oil.

$^1$H NMR (392 MHz, $CDCl_3$, δ): 0.87 (t, *J* = 7.1 Hz, 3H), 1.19–1.40 (m, 4H), 1.83–2.06 (m, 4H), 2.16–2.27 (m, 2H), 3.74 (t, *J* = 7.1 Hz, 2H), 5.36–5.49 (m, 1H), 5.71 (tdt, *J* = 1.8, 7.8, 11.8 Hz, 1H),

7.70–7.76 (m, 2H), 7.82–7.89 (m, 2H). $^{13}$C NMR (99 MHz, $CDCl_3$, δ): 13.6 (*C*$H_3$), 21.6 (t, *J* = 3.8 Hz, *C*$H_2$), 22.0 (*C*$H_2$), 27.7 (*C*$H_2$), 31.2 (*C*$H_2$), 35.7 (t, *J* = 27.8 Hz, *C*$H_2$), 37.1 (*C*$H_2$), 121.9 (t, *J* = 240.8 Hz, *C*), 122.9 (*C*H), 124.0 (t, *J* = 26.9 Hz, *C*H), 131.7 (*C*), 133.7 (*C*H), 138.2 (t, *J* = 6.1 Hz, *C*H), 167.9 (*C*). $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –91.4 (d, *J* = 22.8 Hz, 2F). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{18}H_{21}O_2NF_2Na$, 344.1433; found, 344.1434.

**Preparation of (*Z*)-(8-chloro-3,3-difluorooct-4-en-1-yl)benzene [(*Z*)-1g].[18]**




In a vacuum dried 200 mL round bottomed flask, *n*-BuLi (1.6 M hexane solution, 13.8 mL) was added dropwise to the mixture of 5-chloropent-1-yne (2.09 mL, 20 mmol) and dry THF (30 mL) at –78 ºC under a nitrogen atmosphere. After the 30 minutes, $PhC_2H_5CHO$ (2.63 mL, 20 mL) was added dropwise to the reaction mixture, then allowed to warm to room temperature and stirred for 19 hours. The reaction mixture was quenched by aqueous $NH_4Cl$ at 0 ºC and 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 used in the subsequent reaction without further purification.

In a vacuum dried 200 mL round bottomed flask, $MnO_2$ (52.1 g, 600 mmol) was dissolved in $CH_2Cl_2$ (50 mL). The alcohol was then added dropwise to the reaction mixture. After the mixture was stirred for 18 hours at room temperature, $CH_2Cl_2$ (100 mL) was added and the reaction mixture was filtered through a Celite pad. After the removal of the solvent, the crude product was purified by flash column chromatography ($SiO_2$, EtOAc/Hexane 0:100–15:85) to give the corresponding ketone (2.72 g, 58% yield) as a colorless oil.

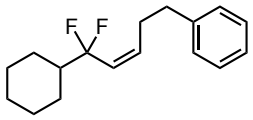
In a vacuum dried 50 mL round bottomed flask, DAST (3.82 mL, 29 mmol) was added by one portion to the corresponding ketone (2.72 g, 11.6 mmol) at 0 ºC. EtOH (1 drop) was added and the mixture was stirred for 8 h at 60 ºC. $CH_2Cl_2$ (20 mL) was then added and the reaction mixture was carefully quenched by aqueous $NH_4Cl$ at 0 ºC and extracted with $CH_2Cl_2$. The crude product was purified by flash column chromatography ($SiO_2$, Hexane only) to give the corresponding difluoro compound (1.76 g, 59% yield) as a brown oil.

In a vacuum dried 50 mL round bottomed flask, Lindlar catalyst (592.3 mg, 0.28 mmol) was dissolved in EtOH (100 mL) and quinoline (165.0 μL, 1.39 mmol) was added to this mixture. The

corresponding difluoro compound (1.76 g, 5.6 mmol) was then added to the mixture and stirred for 2 h under $H_2$ atomosphere ($H_2$ baloon). The reaction mixture was then filtered through a Celite pad and concentrated under reduced pressure. The crude product was purified by flash column chromatography ($SiO_2$, Hexane only). (*Z*)-**1g** was obtained in 43% yield (0.62 g, 2.4 mmol) as a colorless oil.

$^1$H NMR (401 MHz, $CDCl_3$, δ): 1.90 (dt, *J* = 7.1, 14.0 Hz, 2H), 2.16–2.30 (m, 2H), 2.40–2.49 (m, 2H), 2.77–2.85 (m, 2H), 3.56 (t, *J* = 6.6 Hz, 2H), 5.51–5.63 (m, 1H), 5.69–5.78 (m, 1H), 7.17–7.33 (m, 5H).$^{13}$C NMR (100 MHz, $CDCl_3$, δ): 25.6 (*C*$H_2$), 28.5 (*C*$H_2$), 32.1 (*C*$H_2$), 40.2 (*t*, *J* = 26.7 Hz, *C*$H_2$), 44.1 (*C*$H_2$), 121.9 (t, *J* = 238.8 Hz, *C*), 125.8 (t, *J* = 26.7 Hz, *C*H), 126.1 (*C*H), 128.2 (*C*H), 128.4 (*C*H), 136.1 (t, *J* = 5.8 Hz, *C*H), 140.4 (*C*). $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –92.3 (s, 2F). HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{14}H_{17}ClF_2$, 258.0987; found, 258.0987.

**(*Z*)-(5-cyclohexyl-5,5-difluoropent-3-en-1-yl)benzene [(*Z*)-1i].**

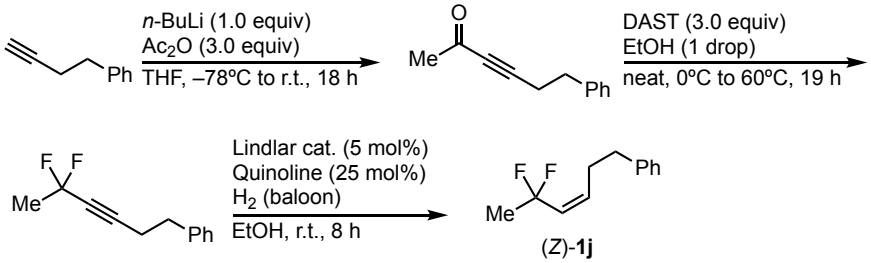



(*Z*)-**1i**

(*Z*)-**1h** was prepared from the corresponding alkyne and aldehyde according to the procedure described above.

$^1$H NMR (396 MHz, $CDCl_3$, δ): 1.03–1.26 (m, 5H), 1.60–1.85 (m, 6H), 2.53–2.62 (m, 2H), 2.71 (t, *J* = 7.5 Hz, 2H), 5.34–5.48 (m, 1H), 5.71–5.80 (m, 1H), 7.14–7.23 (m, 3H), 7.24–7.33 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$, δ): 25.6 (*C*$H_2$), 25.9 (*C*$H_2$), 30.2 (*C*$H_2$), 35.7 (*C*$H_2$), 45.7 (t, *J* = 25.4 Hz, *C*H), 123.7 (t, *J* = 242.9 Hz, *C*), 124.1 (t, *J* = 27.3 Hz, *C*H), 125.9 (*C*H), 128.3 (*C*H), 128.4 (*C*H), 136.6 (t, *J* = 5.8 Hz, *C*H), 141.3 (*C*). $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –99.3 (t, *J* = 15.5 Hz, 2F). HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{17}H_{22}F_2$, 264.1690; found, 264.1691.

**Preparation of (*Z*)-(5,5-difluorohex-3-en-1-yl)benzene [(*Z*)-1j].[18]**




(*Z*)-**1j**

In a vacuum dried 200 mL round bottomed flask, *n*-BuLi (1.6 M hexane solution, 12.5 mL) was added dropwise to the mixture of 3-butyn-1-ylbenzene (2.77 mL, 20 mmol) and dry THF (30 mL) at –78 ºC under a nitrogen atmosphere. After 30 minutes, $Ac_2O$ (5.62 mL, 60 mmol) was added dropwise

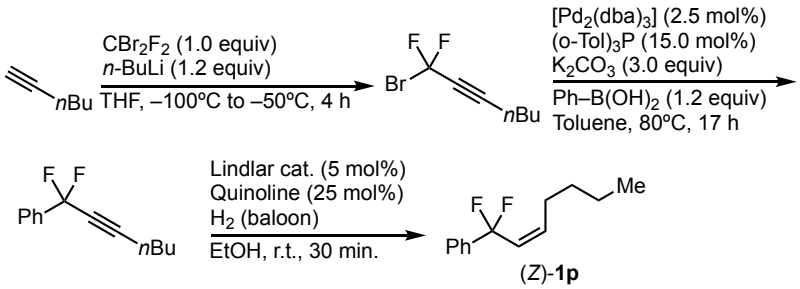
to the reaction mixture. The reaction mixture was warmed up to room temperature over the course of 18 h. The reaction mixture was then quenched by aqueous $NH_4Cl$ at 0 ºC and extracted with $Et_2O$ three times. The combined organic layer was dried over $MgSO_4$. After filtration, the solvent was removed by evaporation under reduced pressure. The crude product was purified by flash column chromatography ($SiO_2$, EtOAc/Hexane 0:100–10:70) to give the corresponding ketone (3.11 g, 90% yield) as a colorless oil.

In a vacuum dried 50 mL round bottomed flask, DAST (5.80 mL, 45.0 mmol) was added by one portion to the corresponding ketone (2.58 g, 15.0 mmol) at 0ºC. EtOH (1 drop) was added and the mixture was stirred for 19 h at 60ºC. After that, $CH_2Cl_2$ (40 mL) was added and the reaction mixture was carefully quenched by aqueous $NH_4Cl$ at 0ºC and extracted with $CH_2Cl_2$. The crude product was purified by flash column chromatography ($SiO_2$, EtOAc/Hexane 0:100–7:93) to give the corresponding difluoro-containing compound (1.28 g, 42% yield) as a brown oil.

In a vacuum dried 200 mL round bottomed flask, Lindlar catalyst (319.3 g, 0.15 mmol) was dissolved in EtOH (60 mL) and quinoline (88.9 μL, 0.75 mmol) was added to this mixture. Then, the corresponding difluoro-containing compound (582.6 mg, 3.0 mmol) was added to this mixture and stirred for 8 h under $H_2$ atomosphere ($H_2$ baloon). The reaction mixture was then filtered through a Celite pad and concentrated under reduced pressure. The crude product was purified by flash column chromatography ($SiO_2$, Hexane only). (*Z*)-**1j** was obtained in 58% yield (341.6 mg, 1.74 mmol) as a colorless oil.

$^1$H NMR (399 MHz, $CDCl_3$, δ): 1.62 (t, $J$ = 18.0 Hz, 3H), 2.55–2.61 (m, 2H), 2.72 (t, $J$ = 7.6 Hz, 2H), 5.48–5.58 (m, 1H), 5.72 (tdt, $J$ = 1.8, 7.6, 11.5 Hz, 1H), 7.18–7.22 (m, 3H), 7.27–7.31 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$, δ): 25.3 (t, $J$ = 29.3 Hz, *C*H$_3$), 29.9 (*C*H$_2$), 35.5 (*C*H$_2$), 121.4 (t, $J$ = 233.1 Hz, *C*), 126.0 (*C*H), 126.2 (t, $J$ = 26.9 Hz, *C*H), 128.3 (*C*H), 128.4 (*C*H), 136.1 (t, $J$ = 6.1 Hz, *C*H), 141.2 (*C*). $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –84.1 (d, $J$ = 22.8 Hz, 2F). HRMS–EI ($m/z$): $[M]^+$ calcd for $C_{11}H_{14}F_2$, 196.1064; found, 196.1061.

**Preparation of (*Z*)-(1,1-difluorohept-2-en-1-yl)benzene [(*Z*)-1p].[19,20]**




To a solution of hex-1-yne (5.7 mL, 50 mmol) in THF (250 mL), a solution of *n*-BuLi (1.6 M in hexane, 31.3 mL) was added dropwise at –90 °C. After the reaction mixture had been stirred for 30 min at that temperature, the reaction mixture was cooled to –110 °C. Cold $CF_2Br_2$ (–78°C) (5.5 mL, 60 mmol) was added to the mixture. After the addition was complete, the mixture allowed to warm to

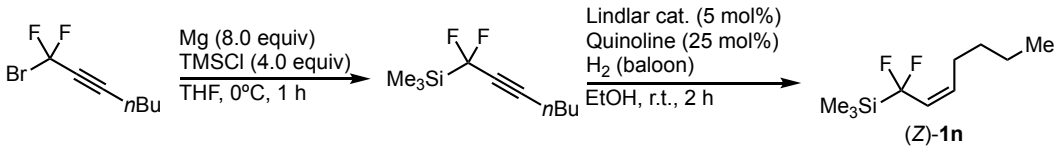
–50 °C with stirring for 3 h and was quenched with aqueous $NH_4Cl$ solution. The aqueous layer was extracted with $Et_2O$ and the organic layer was washed with $H_2O$. The organic layer was dried over $Na_2SO_4$. After evaporation of the solvent, the crude product was purified by distillation to afford the corresponding difluoro compound in 73% yield (7.69 g, 36.5 mmol).

To a solution of $[Pd_2(dba)_3]$ (207.1 mg, 0.25 mmol), (*o*-Tol)$_3$P (456.6 mg, 1.5 mmol), $K_2CO_3$ (4.15 g, 30 mmol) and $PhB(OH)_2$ (1.46 g, 12 mmol) in Toluene (66 mL), the corresponding difluoro compound (2.15 g, 10 mmol) was added dropwise. Then, the reaction mixture was stirred at 80 ºC for 17 h. The mixture was then extracted with $Et_2O$ and the organic layer was washed with $H_2O$. The organic layer was dried over $MgSO_4$. After evaporation of the solvent, the crude product was purified by flash column chromatography ($SiO_2$, Hexane only) to afford the coupling product in 53% yield (1.30 g, 6.2 mmol) as a colorless oil.

In a vacuum dried 200 mL round bottomed flask, Lindlar catalyst (564 mg, 0.27 mmol) was dissolved in EtOH (100 mL) and quinoline (158 μL, 1.33 mmol) was added to this mixture. Then, the corresponding difluoro compound (1.11 g, 5.3 mmol) was added to this mixture and stirred for 30 minutes under $H_2$ atomosphere ($H_2$ baloon). The reaction mixture was then filtered through a Celite pad and concentrated under reduced pressure. The crude product was purified by flash column chromatography ($SiO_2$, Hexane only) and gel-permeation chromatography. (*Z*)-**1p** was obtained in 53% yield (591.7 mg, 2.8 mmol) as a colorless oil.

$^1$H NMR (401 MHz, $CDCl_3$, δ): 0.83 (t, *J* = 7.0 Hz, 3H), 1.20–1.37 (m, 4H), 2.10–2.20 (m, 2H), 5.72–5.87 (m, 2H), 7.37–7.46 (m, 3H), 7.51–7.58 (m, 2H). $^{13}$C NMR (99 MHz, $CDCl_3$, δ): 13.8 (*C*H$_3$), 22.2 (*C*H), 28.1 (*C*H$_2$), 31.3 (*C*H$_2$), 120.0 (t, *J* = 242.3 Hz, *C*), 125.3 (t, *J* = 29.6 Hz, *C*H), 125.3 (t, *J* = 5.3 Hz, *C*H), 128.4 (*C*H), 129.8 (*C*H), 138.0 (t, *J* = 28.2 Hz, *C*), 138.8 (t, *J* = 7.2 Hz, *C*H). $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –85.2 (s, 2F). HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{13}H_{16}F_2$, 210.1220; found, 210.1224.

**Preparation of (*Z*)-(1,1-difluorohept-2-en-1-yl)trimethylsilane [(*Z*)-1n].[21]**



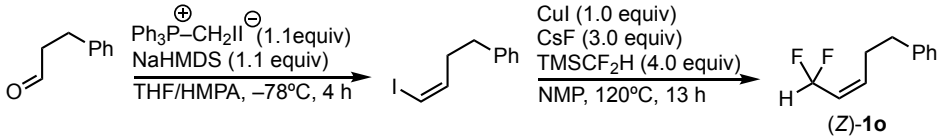

TMSCl (3.03 mL, 24 mmol) was added to a solution of activated Mg (1.17 g, 48 mmol) in THF (60 mL) at 0 ºC. After 1 h, the propargyl bromide (1.26 g, 6.0 mmol) was added dropwise to the reaction mixture. The reaction mixture was then stirred at 0 ºC for 1 h. The mixture was filtered, extracted with $Et_2O$ and the organic layer was washed with $H_2O$, then the organic layer was dried over $MgSO_4$. After evaporation of the solvent, the crude product was purified by flash column chromatography ($SiO_2$,

Hexane only) to afford the silylated compound in 51% yield (627.5 mg, 3.1 mmol) as a colorless oil.

In a vacuum dried 100 mL round bottomed flask, Lindlar catalyst (266.1 mg, 0.125 mmol) was dissolved in EtOH (50 mL). Quinoline (74.1 μL, 0.63 mmol) was then added to the mixture. The corresponding silylated compound (520.6 mg, 2.5 mmol) was added to the mixture and stirred for 30 minutes under $H_2$ atomosphere ($H_2$ baloon). The reaction mixture was then filtered through a Celite pad and concentrated under reduced pressure. The crude product was purified by flash column chromatography ($SiO_2$, Hexane only) and gel-permeation chromatography. (*Z*)-**1n** was obtained in 44% yield (232.0 mg, 1.1 mmol) as a colorless oil.

$^1$H NMR (401 MHz, $CDCl_3$, δ): 0.16 (s, 9H), 0.90 (t, *J* = 6.8 Hz, 3H), 1.24–1.43 (m, 4H), 2.15–2.26 (m, 2H), 5.29–5.46 (m, 1H), 5.59–5.70 (m, 1H). $^{13}$C NMR (99 MHz, $CDCl_3$, δ): –4.9 (*C*H$_3$), 13.9 (*C*H$_3$), 22.4 (*C*H), 28.5 (*C*H$_2$), 32.1 (*C*H$_2$), 124.5 (t, *J* = 20.3 Hz, *C*), 128.9 (t, *J* = 260.6 Hz, *C*H), 136.2 (t, *J* = 8.5 Hz, *C*H). $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –109.2 (d, *J* = 23.1, 2F). HRMS–FI (*m*/*z*): $[M]^+$ calcd for $C_{10}H_{20}F_2Si$, 206.1302; found, 206.1309.

**Preparation of (*Z*)-(5,5-difluoropent-3-en-1-yl)benzene [(*Z*)-1o].[22]**



(*Z*)-**1o**

Sodium hexamethyldisilazide (NaHMDS) (3.03 mL, 24 mmol) was added to a solution of the ylide (15.8 g, 29.9 mmol) in THF (110 mL) at room temperature. After the solution was cooled to –78 ºC, hexamethylphosphoric triamide (HMPA) (420 μL) was added to the reaction mixture. The aldehyde (3.50 mL, 23.9 mmol) was added dropwise and the reaction mixture was stirred at –78 ºC for 1 h. The mixture was then allowed to warm to room temperature and stirred for 1h. Then, the reaction mixture was quenched by cold brine, extracted with pentane three times, and the organic layer was washed with $H_2O$. After the organic layer was dried over $MgSO_4$ and evaporation of the solvent, the crude product was purified by flash column chromatography ($SiO_2$, Hexane only) to afford the compound in 21% yield (1.35 g, 5.0 mmol) as a colorless oil.

CuI (1.24 g, 6.5 mmol) and CsF (2.96 g, 19.5 mmol) were dissolved in *N*-methylpyrrolidone (NMP) (32.5 mL). The corresponding vinyl iodide (1.82 g, 6.5 mmol) and $TMSCF_2H$ (3.23 g, 4.0 mmol) were added to the reaction mixture. The mixture was stirred at 120 ºC for 17 h and was quenched with aqueous $NH_4Cl$ solution. The mixture was extracted with $Et_2O$ and washed with $H_2O$ three times, then the organic layer was dried over $MgSO_4$. After evaporation of the solvent, the crude product was purified by flash column chromatography ($SiO_2$, Hexane only) to afford (*Z*)-**1o** in 39% yield (465.2 mg, 2.5 mmol) as a colorless oil.

$^1$H NMR (401 MHz, $CDCl_3$, δ): 2.46–2.55 (m, 2H), 2.74 (t, *J* = 7.6 Hz, 2H), 5.54–5.65 (m, 1H), 5.86–5.95 (m, 1H), 6.28 (td, *J* = 6.8, 55.7 Hz, 1H), 7.16–7.24 (m, 3H), 7.28–7.33 (m, 2 H). $^{13}$C NMR (99

MHz, $CDCl_3$, δ): 29.6 (*C*$H_2$), 35.2 (*C*$H_2$), 111.8 (t, *J* = 230.7 Hz, *C*H), 123.3 (t, *J* = 24.9 Hz, *C*H), 126.2 (*C*H), 128.3 (*C*H), 128.4 (*C*H), 138.5 (t, *J* = 12.0 Hz, *C*H), 140.6 (*C*). $^{19}F$ NMR (373 MHz, $CDCl_3$, δ): –111.4 (d, *J* = 57.1 Hz, 2F). HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{11}H_{12}F_2$, 182.0907; found, 182.0907.

## General Borylation and Derivatization Procedures

**Procedure for the copper(I)-catalyzed enantioselective boryl substitution of (*Z*)-1a (Scheme 2, Condition A).**

Copper chloride (2.5 mg, 0.025 mmol) and bis(pinacolato)diboron (190.0 mg, 0.75 mmol), (*R*,*R*)-BenzP* (7.1 mg, 0.025 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. Dry THF (1.0 mL) was added in the vial through the rubber septum using a syringe. After stirring for 30 min at 30 ºC, (*Z*)-**1a** (120.1 mg, 0.50 mmol) was added to the mixture at 30 ºC. After the reaction was completed, 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 **2a** as a colorless oil.

**Procedure for the oxidation of the borylation product to determine the er value by HPLC analysis.**

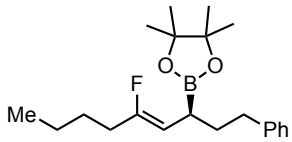
In a reaction vial, the borylation product (0.1 mmol) was dissolved in THF/$H_2O$ (1:1, 1.0 mL). $NaBO_3$•$4H_2O$ (76.9 mg, 0.5 mmol) was then added to the mixture at room temperature. After stirred for 2 hours, the reaction mixture was extracted with $Et_2O$. The organic layer was dried over $MgSO_4$. After filtration, the crude mixture was purified by flash column chromatography ($SiO_2$, ethyl acetate/hexane, typically 5:95–15:85) to afford the corresponding alcohol.

**Procedure for the esterification of the borylation product to determine the er value by HPLC analysis.**

The alcohol was obtained through the oxidation of the borylation product according to the procedure described above. In a reaction vial, the obtained alcohol (0.1 mmol) and DMAP (0.05 mmol) was dissolved in $CH_2Cl_2$ (2.0 mL). $Et_3N$ (28.0 μL, 0.2 mmol) and *p*-nitrobenzoyl chloride (27.8 mg, 0.15 mmol) were then added to the mixture at room temperature. After stirred for 3 hours, 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 ($SiO_2$, ethyl acetate/hexane, typically 0:100–4:96) to give the corresponding ester.

## Borylation Product Characterizations

**(*S*,*Z*)-2-(5-fluoro-1-phenylnon-4-en-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane [(*S*,*Z*)-2a].**

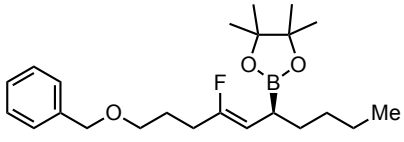



(*S*,*Z*)-**2a**

The reaction was conducted for 2 h with 120.1 mg (0.50 mmol) of (*Z*)-**1a.** The product (*S,Z*)-**2a** was obtained in 93% yield (160.2 mg) with 97/3 er. The stereoselectivity of (*S*,*Z*)-**2a** was determined by GC analysis (*Z*/*E* = 95/5).

$^{1}$H NMR (392 MHz, $CDCl_3$, δ): 0.91 (t, *J* = 7.3 Hz, 3H), 1.24 (s, 12H), 1.35 (dq, *J* = 7.2, 14.6 Hz, 2H), 1.43–1.52 (m, 2H), 1.58–1.70 (m, 1H), 1.77–1.89 (m, 1H), 2.11–2.22 (m, 3H), 2.49–2.71 (m, 2H), 4.50 (dd, *J* = 9.4, 38.4 Hz, 1H), 7.13–7.20 (m, 3H), 7.23–7.29 (m, 2H). $^{13}$C NMR (99 MHz, $CDCl_3$, δ): 13.7 (*C*$H_3$), 19.9 (br, B–*C*H), 21.8 (*C*$H_2$), 24.56 (*C*$H_3$), 24.63 (*C*$H_3$), 28.4 (*C*$H_2$), 31.7 (d, *J* = 28.3 Hz, *C*$H_2$), 33.2 (*C*$H_2$), 35.4 (*C*$H_2$), 83.1 (*C*), 105.3 (d, *J* = 16.1 Hz, *C*H), 125.5 (*C*H), 128.1 (*C*H), 128.4 (*C*H), 142.6 (*C*), 159,4 (d, *J* = 253.9 Hz, *C*). $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –108.9 – –108.7 (m, 1F). HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{21}H_{32}BFO_2$, 346.2483; found, 346.2481. $[\alpha]_D^{18.8}$ +0.35 (*c* 1.60, $CHCl_3$). The er value was determined by HPLC analysis of the corresponding alcohol after oxidation of the boryl group. Daicel CHIRALPAK® IC-3, 2-PrOH/Hexane = 4/96, 0.5 mL/min, 40°C, retention time: 18.88 min [(*Z*)-alcohol major enantiomer], 16.37 min [(*Z*)-alcohol minor enantiomer], and 13.88 min [(*E*)-alcohol major enantiomer]. Minor enantiomer of (*E*)-alcohol was not detected by HPLC analysis.

**(*S*,*Z*)-2-(10-(benzyloxy)-7-fluorodec-6-en-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane [(*S*,*Z*)-2c].**



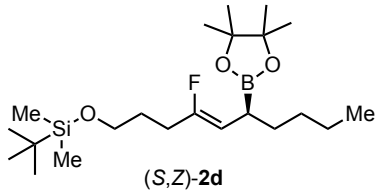

(*S*,*Z*)-**2c**

The reaction was conducted for 1.5 h with 141.1 mg (0.50 mmol) of (*Z*)-**1c.** The product (*S,Z*)-**2c** was obtained in 92% yield (180.0 mg) with 96:4 er. The stereoselectivity of (*S,R*)-**2c** was determined by GC analysis (*Z*/*E* = 94/6).

$^{1}$H NMR (392 MHz, $CDCl_3$, δ): 0.87 (t, *J* = 6.9 Hz, 3H), 1.18–1.55 (m, 18H), 1.80 (quin, *J* = 7.0 Hz, 2H), 2.08 (q, *J* = 8.0 Hz, 1H), 2.26 (dt, *J* = 7.4, 17.9 Hz, 2H), 3.50 (t, *J* = 6.3 Hz, 2H), 4.47 (dd, *J* = 9.8, 38.4 Hz, 1H), 4.50 (s, 2H), 7.27–7.37 (m, 5H). $^{13}$C NMR (99 MHz, $CDCl_3$, δ): 14.0 (*C*$H_3$), 19.9 (br, B–*C*H), 22.5 (*C*$H_2$), 24.5 (*C*$H_3$), 24.6 (*C*$H_3$), 26.5 (*C*$H_2$), 28.7 (d, *J* = 29.3 Hz, *C*$H_2$), 30.7 (*C*$H_2$),

31.2 (*C*$H_2$), 69.0 (*C*$H_2$), 72.8 (*C*$H_2$), 82.9 (*C*), 106.3 (d, *J* = 17.0 Hz, *C*H), 127.4 (*C*H), 127.5 (*C*H), 128.2 (*C*H), 138.4 (*C*), 158.2 (d, *J* = 253.0 Hz, *C*). $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –110.0 – –110.2 (m, 1F). HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{23}H_{37}O_3BF$, 391.2819; found, 391.2818. $[\alpha]_D^{21.9}$ +1.2 (*c* 1.02, $CHCl_3$). The er value was determined by HPLC analysis of the corresponding alcohol after oxidation of the boryl group. Daicel CHIRALPAK® IBN-3, 2-PrOH/Hexane = 2/98, 0.5 mL/min, 40°C, retention time: 34.69 min [(*Z*)-alcohol major enantiomer], 31.64 min [(*Z*)-alcohol minor enantiomer] and 27.26 min [(*E*)-alcohol major enantiomer]. Minor enantiomer of (*E*)-alcohol was not detected by HPLC analysis.

**(*S*,*Z*)-*tert*-butyl((4-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)dec-4-en-1-yl)oxy)dimethylsilane [(*S*,*Z*)-2d].**

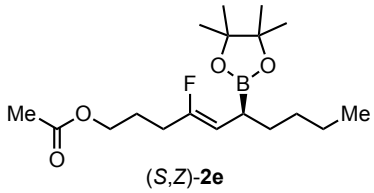


(*S*,*Z*)-**2d**

The reaction was conducted for 1.5 h with 157.4 mg (0.51 mmol) of (*Z*)-**1d.** The product (*S,Z*)-**2d** was obtained in 99% yield (200.1 mg) with 96:4 er. The stereoselectivity of (*S,Z*)-**2d** was determined by GC analysis (*Z*/*E* = 95/5).

$^1$H NMR (392 MHz, $CDCl_3$, δ): 0.04 (s, 6H), 0.84–0.93 (m, 12H), 1.18–1.55 (m, 18H), 1.69 (quin, *J* = 6.9 Hz, 2H), 2.08 (q, *J* = 8.0 Hz, 1H), 2.22 (dt, *J* = 7.4, 17.9 Hz, 2H), 3.62 (t, *J* = 6.3 Hz, 2H), 4.46 (dd, *J* = 9.8, 38.4 Hz, 1H). $^{13}$C NMR (99 MHz, $CDCl_3$, δ): –5.4 (*C*$H_3$), 14.0 (*C*$H_3$), 18.3 (*C*), 20.0 (br, B–*C*H), 22.6 (*C*$H_2$), 24.59 (*C*$H_3$), 24.62 (*C*$H_3$), 25.9 (*C*$H_3$), 28.4 (d, *J* = 28.8 Hz, *C*$H_2$), 29.5 (*C*$H_2$), 30.8 (*C*$H_2$), 31.3 (*C*$H_2$), 61.9 (*C*$H_2$), 83.0 (*C*), 106.1 (d, *J* = 16.3 Hz, *C*H), 158.6 (d, *J* = 252.9 Hz, *C*). $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –109.5 – –109.7 (m, 1F). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{22}H_{44}O_3BFNaSi$, 437.3033; found, 437.3030. $[\alpha]_D^{21.7}$ +1.1 (*c* 1.55, $CHCl_3$). The er value was determined by HPLC analysis of the corresponding alcohol after oxidation of the boryl group. Daicel CHIRALPAK® IC-3, 2-PrOH/Hexane = 1.5/98.5, 0.5 mL/min, 40°C, retention time: 15.97 min [(*Z*)-alcohol major enantiomer], 14.87 min [(*Z*)-alcohol minor enantiomer], 12.59 min [(*E*)-alcohol major enantiomer], and 13.46 min [(*E*)-alcohol minor enantiomer].

**(*S*,*Z*)-4-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)dec-4-en-1-yl acetate [(*S*,*Z*)-2e].**

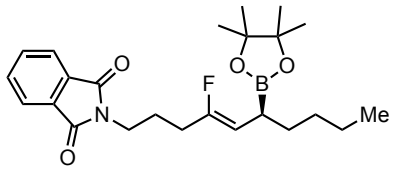


(*S*,*Z*)-**2e**

The reaction was conducted for 2 h with 117.2 mg (0.50 mmol) of (*Z*)-**1e.** The product (*S,Z*)-**2e** was obtained in 90% yield (153.2 mg) with 96:4 er. The stereoselectivity of (*S,Z*)-**2e** was determined by GC analysis (*Z*/*E* = 90/10).

$^{1}$H NMR (396 MHz, $CDCl_3$, δ): 0.87 (t, *J* = 7.0 Hz, 3H), 1.16–1.56 (m, 18H), 1.82 (quin, *J* = 7.0 Hz, 2H), 2.05–2.12 (m, 4H), 2.24 (dt, *J* = 7.5, 17.9 Hz, 2H), 4.09 (t, *J* = 6.6 Hz, 2H), 4.50 (dd, *J* = 7.5, 17.9 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$, δ): 13.9 (*C*H$_3$), 19.9 (br, B–*C*H), 20.8 (*C*H$_3$), 22.5 (*C*H$_2$), 24.5 (*C*H$_3$), 25.4 (*C*H$_2$), 28.5 (d, *J* = 28.7 Hz, *C*H$_2$), 30.7 (*C*H$_2$), 31.2 (*C*H$_2$), 63.3 (*C*H$_2$), 83.0 (*C*), 106.8 (d, *J* = 16.3 Hz, *C*H), 157.4 (d, *J* = 252.9 Hz, *C*), 170.9 (*C*). $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –110.6 (t, *J* = 22.8 Hz, 1F). HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{18}H_{32}O_4BF$, 342.2381; found, 342.2382. $[\alpha]_D^{21.8}$ +1.2 (*c* 1.09, $CHCl_3$). The er value was determined by HPLC analysis of the corresponding alcohol after oxidation of the boryl group. Daicel CHIRALPAK® IF-3, 2-PrOH/Hexane = 4/96, 0.5 mL/min, 40 °C, retention time: 36.06 min [(*Z*)-alcohol major enantiomer], 35.01 min [(*Z*)-alcohol minor enantiomer] and 53.45 min [(*E*)-alcohol major enantiomer]. Minor enantiomer of (*E*)-alcohol was not detected by HPLC analysis.

**(*S*,*Z*)-2-[4-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)dec-4-en-1-yl]isoindoline-1,3-dione [(*S*,*Z*)-2f].**



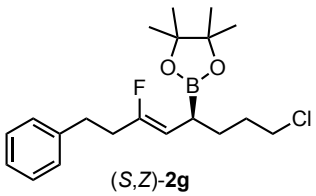
(*S*,*Z*)-**2f**

The reaction was conducted for 1.5 h with 160.0 mg (0.50 mmol) of (*Z*)-**1f.** The product (*S,Z*)-**2f** was obtained in 56% yield (119.4 mg) with 95:5 er. The stereoselectivity of (*S,Z*)-**2f** was determined by GC analysis (*Z*/*E* = 96/4).

$^{1}$H NMR (396 MHz, $CDCl_3$, δ): 0.87 (t, *J* = 5.8 Hz, 3H), 1.01–1.54 (m, 18H), 1.87 (quin, *J* = 7.0 Hz, 2H), 2.07 (q, *J* = 8.0 Hz, 1H), 2.22 (dt, *J* = 8.0, 16.0 Hz, 2H), 3.72 (t, *J* = 7.2 Hz, 2H), 4.52 (dd, *J* = 9.6, 38.5 Hz, 1H), 7.65–7.73 (m, 2H), 7.78–7.86 (m, 2H). $^{13}$C NMR (99 MHz, $CDCl_3$, δ): 14.0 (*C*H$_3$), 19.8 (br, B–*C*H), 22.5 (*C*H$_2$), 24.5 (*C*H$_3$), 24.6 (*C*H$_3$), 25.5 (*C*H$_2$), 29.6 (d, *J* = 28.3 Hz, *C*H$_2$), 30.7 (*C*H$_2$), 31.2 (*C*H$_2$), 83.0 (*C*), 106.7 (d, *J* = 17.0 Hz, *C*H), 123.1 (*C*H), 132.0 (*C*), 133.8 (*C*H), 157.4 (d,

*J* = 255.0 Hz, *C*), 168.2 (*C*). $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –109.9 – –110.1 (m, 1F). HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{24}H_{33}O_4BFN$, 429.2491; found, 429.2475. $[\alpha]_D^{21.7}$ +0.66 (*c* 1.14, $CHCl_3$). The er value was determined by HPLC analysis of the boryl group. Daicel CHIRALPAK® IE-3, 2-PrOH/Hexane = 1.5/98.5, 0.5 mL/min, 40 °C, retention time: 32.78 min [(*Z*)-**2f** major enantiomer], 29.56 min [(*Z*)-**2f** minor enantiomer], 25.84 min [(*E*)-**2f** major enanomer] and 27.53 min [(*E*)-**2f** minor enantiomer].

**(*S*,*Z*)-2-(1-chloro-6-fluoro-8-phenyloct-5-en-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane [(*S*,*Z*)-2g].**

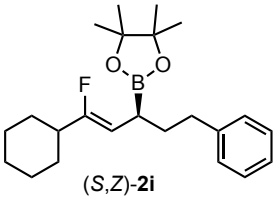


(*S*,*Z*)-**2g**

The reaction was conducted for 1 h with 129.4 mg (0.50 mmol) of (*Z*)-**1g.** The product (*S,Z*)-**2g** was obtained in 93% yield (170.0 mg) with 93.5:6.5 er. The stereoselectivity of (*S,Z*)-**2g** was determined by GC analysis (*Z*/*E* = 94/6).

$^1$H NMR (396 MHz, $CDCl_3$, δ): 1.23 (s, 12H), 1.34–1.46 (m, 1H), 1.58–1.73 (m, 3H), 2.08 (td, *J* = 5.7, 9.6 Hz, 1H), 2.36–2.56 (m, 2H), 2.80 (t, *J* = 7.7 Hz, 2H), 3.47 (t, *J* = 6.5 Hz, 2H), 4.42 (dd, *J* = 10.1, 38.2 Hz, 1H), 7.16–7.22 (m, 3H), 7.24–7.31 (m, 2H). $^{13}$C NMR (99 MHz, $CDCl_3$, δ): 19.2 (br, B–*C*H), 24.60 (*C*$H_3$), 24.63 (*C*$H_3$), 28.2 (*C*$H_2$), 31.8 (*C*$H_2$), 32.6 (*C*$H_2$), 33.9 (d, *J* = 27.7 Hz, *C*$H_2$), 45.0 (*C*$H_2$), 83.0 (*C*), 105.9 (d, *J* = 15.3 Hz, *C*H), 126.0 (*C*H), 128.3 (*C*H), 128.4 (*C*H), 158.5 (d, *J* = 253.0 Hz, *C*). $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –110.2 – –110.0 (m, 1F). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{20}H_{29}O_2BClFNa$, 389.1829; found, 389.1831. $[\alpha]_D^{17.7}$ +1.3 (*c* 0.94, $CHCl_3$). The er value was determined by HPLC analysis of the corresponding alcohol after oxidation of the boryl group. Daicel CHIRALPAK® IBN-3, 2-PrOH/Hexane = 5/95, 0.5 mL/min, 40°C, retention time: 21.83 min [(*Z*)-alcohol major enantiomer], 27.77 min [(*Z*)-alcohol minor enantiomer], 17.53 min [(*E*)-alcohol major enantiomer], and 23.13 min [(*E*)-alcohol minor enantiomer].

**(*S*,*Z*)-2-(1-cyclohexyl-1-fluoro-5-phenylpent-1-en-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane [(*S*,*Z*)-2i].**

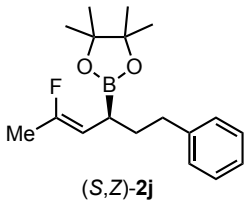



(*S*,*Z*)-**2i**

The reaction was conducted for 1 h with 132.2 mg (0.50 mmol) of (*Z*)-**1i.** The product (*S,Z*)-**2i** was obtained in 95% yield (176.0 mg) with 97:5 er. The stereoselectivity of (*S,Z*)-**2i** was determined by GC analysis (*Z*/*E*= >98/2).

$^{1}$H NMR (392 MHz, $CDCl_3$, δ): 1.11–1.31 (m, 18H), 1.56–1.69 (m, 1H), 1.71–1.88 (m, 5H), 2.00–2.17 (m, 2H), 2.47–2.70 (m, 2H), 4.46 (dd, *J* = 9.6, 39.4 Hz, 1H), 7.12–7.19 (m, 3H), 7.22–7.28 (m, 2H). $^{13}$C NMR (99 MHz, $CDCl_3$, δ): 19.7 (br, B–*C*H), 24.5 (*C*$H_3$), 24.6 (*C*$H_3$), 25.8 (*C*$H_2$), 26.0 (*C*$H_2$), 30.1 (*C*$H_2$), 33.2 (*C*$H_2$), 35.4 (*C*$H_2$), 40.5 (d, *J* = 26.4 Hz, *C*H), 83.1 (*C*), 103.0 (d, *J* = 17.0 Hz, *C*H), 125.5 (*C*H), 128.1 (*C*H), 128.4 (*C*H), 142.6 (*C*), 163.6 (d, *J* = 255.0 Hz, *C*). $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –112.7 (d, *J* = 22.8 Hz, 1F). HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{23}H_{34}O_2BF$, 372.2640; found, 372.2639. $[\alpha]_D^{20.6}$ +0.44 (*c* 0.90, $CHCl_3$). The er value was determined by HPLC analysis of the corresponding alcohol after oxidation of the boryl group. Daicel CHIRALPAK® IBN-3, 2-PrOH/Hexane = 5/95, 0.5 mL/min, 40°C, retention time: 17.27 min [(*Z*)-alcohol major enantiomer], 18.22 min [(*Z*)-alcohol minor enantiomer].

**(*S*,*Z*)-2-(5-fluoro-1-phenylhex-4-en-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane [(*S*,*Z*)-2j].**



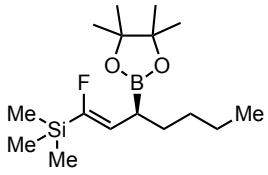

(*S*,*Z*)-**2j**

The reaction was conducted for 4 h with 99.6 mg (0.50 mmol) of (*Z*)-**1j.** The product (*S,Z*)-**2j** was obtained in 86% yield (132.2 mg) with 99:1 er. The stereoselectivity of (*S,Z*)-**2j** was determined by $^{1}$H NMR analysis (*Z*/*E* = 83/17).

$^{1}$H NMR (396 MHz, $CDCl_3$, δ): 1.24 (s, 12H), 1.59–1.70 (m, 1H), 1.77–1.95 (m, 4H), 2.15 (q, *J* = 8.3 Hz, 1H), 2.47–2.76 (m, 2H), 4.51 (dd, *J* = 9.5, 37.6 Hz, 1H), 7.13–7.21 (m, 3H), 7.23–7.31 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$, δ): 17.9 (d, *J* = 30.6 Hz, *C*$H_3$), 20.1 (br, B–*C*H), 24.6 (*C*$H_3$), 24.7 (*C*$H_3$), 33.2 (*C*$H_2$), 35.4 (*C*$H_2$), 83.1 (*C*), 105.8 (d, *J* = 16.3 Hz, *C*H), 125.5 (*C*H), 128.2 (*C*H), 128.4 (*C*H), 142.6 (*C*), 156.0 (d, *J* = 251.0 Hz, *C*). $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –102.4 – –102.1 (m, 1F). HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{18}H_{26}O_2BF$, 303.2046; found, 303.2047. $[\alpha]_D^{21.6}$ +0.07 (*c* 1.00,

$CHCl_3$). The er value was determined by HPLC analysis of the corresponding ester after oxidation of the boryl group and esterification of the alcohol. Daicel CHIRALPAK® IE-3, 2-PrOH/Hexane = 3/97, 0.5 mL/min, 40°C, retention time: 26.46 min [(*Z*)-ester major enantiomer], 23.30 min [(*Z*)-ester minor enantiomer], 16.87 min [(*E*)-ester major enantiomer], and 15.43 min [(*E*)-ester minor enantiomer].

**(*S*,*E*)-[1-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hept-1-en-1-yl]trimethylsilane [(*S*,*E*)-2n].**

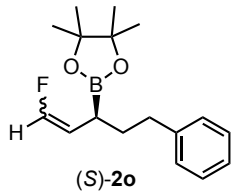



(*S*,*E*)-**2n**

The reaction was conducted for 24 h with 103.2 mg (0.50 mmol) of (*Z*)-**1n.** The product (*S*,*E*)-**2n** was obtained in 30% yield (46.8 mg) with 88.5:11.5 er. The stereoselectivity of (*S*,*E*)-**2n** was determined by GC analysis (*E*/*Z* = >98/2).

$^1$H NMR (401 MHz, $CDCl_3$, δ): 0.13 (s, 9H), 0.87 (t, *J* = 6.8 Hz, 3H), 1.17–1.44 (m, 18H), 2.27 (q, *J* = 8.2 Hz, 1H), 5.00 (dd, *J* = 9.2, 50.1 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$, δ): –2.5 ($CH_3$), 14.0 ($CH_3$), 20.7 (br, B–CH), 22.6 ($CH_2$), 24.5 ($CH_3$), 30.6 ($CH_2$), 31.4 ($CH_2$), 83.0 (*C*), 122.9 (d, *J* = 4.7 Hz, CH), 167.1 (d, *J* = 274.0 Hz, *C*). $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –106.4 (s, 1F). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{16}H_{32}O_2BFNaSi$, 337.2144; found, 337.2142. $[\alpha]_D^{21.9}$ +1.6 (*c* 1.27, $CHCl_3$). The er value was determined by HPLC analysis of the corresponding alcohol after oxidation of the boryl group. Daicel CHIRALPAK® IE-3, 2-PrOH/Hexane = 3/97, 0.5 mL/min, 40°C, retention time: 9.23 min [(*E*)-alcohol major enantiomer], 9.62 min [(*E*)-alcohol minor enantiomer].

**(*S*)-2-(1-fluoro-5-phenylpent-1-en-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane [(*S*)-2o].**

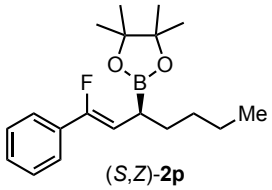



(*S*)-**2o**

The reaction was conducted for 1.5 h with 99.1 mg (0.50 mmol) of (*Z*)-**1o.** The product (*S*)-**2o** was obtained in 95% yield (137.5 mg) with 94:6 er. The stereoselectivity of (*S*)-**2o** was determined by GC analysis (*Z/E* = 50/50).

$^{1}$H NMR (396 MHz, * indicates signals of the isomer, $CDCl_3$, δ): 1.24 (s, 12H), 1.60–1.73 (m, 2H), 1.79–1.93* (m, 2H), 2.27 (td, *J* = 6.2, 9.5 Hz, 1H), 2.50–2.73 (m, 2H), 4.77 (ddd, *J* = 5.0, 10.4, 43.7 Hz, 1H), 5.32–5.42* (m, 1H), 6.38–6.44 (m, 1H), 6.60–6.66* (m, 1H), 7.14–7.20 (m, 3H), 7.24–7.30 (m, 2H). $^{13}$C NMR (100 MHz, * indicates signals of the isomer, $CDCl_3$, δ): 19.5 (br, B–*C*H), 20.6* (br, B–*C*H), 24.6 (*C*$H_3$), 24.7* (*C*$H_3$), 32.78 (*C*$H_2$), 32.84* (*C*$H_2$), 35.0 (*C*$H_2$), 35.3* (*C*$H_2$), 83.3 (*C*), 83.4* (*C*), 111.6 (d, *J* = 5.8 Hz, *C*H), 112.1* (d, *J* = 9.6 Hz, *C*H), 125.6 (*C*H), 125.7* (*C*H), 128.2 (*C*H), 128.3* (*C*H), 128.4 (*C*H), 142.1 (*C*), 142.4* (*C*), 147.4 (d, *J* = 256.7 Hz, *C*H), 148.4* (d, *J* = 254.8 Hz, *C*H). $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –130.6 – –130.2 (m, 1F). HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{17}H_{24}O_2BF$, 290.1857; found, 290.1866. $[\alpha]_D^{21.6}$ +0.07 (*c* 1.16, $CHCl_3$). The er value was determined by HPLC analysis of the corresponding ester after oxidation of the boryl group and esterification of the alcohol. Daicel CHIRALPAK® IBN-3, 2-PrOH/Hexane = 3/97, 0.5 mL/min, 40°C, retention time: 25.33 min [major enantiomer], 32.98 min [minor enantiomer], 24.21 min [isomer major enantiomer], and 29.70 min [isomer minor enantiomer].

**(*S*,*Z*)-2-(1-fluoro-1-phenylhept-1-en-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane [(*S*,*Z*)-2p].**




(*S*,*Z*)-**2p**

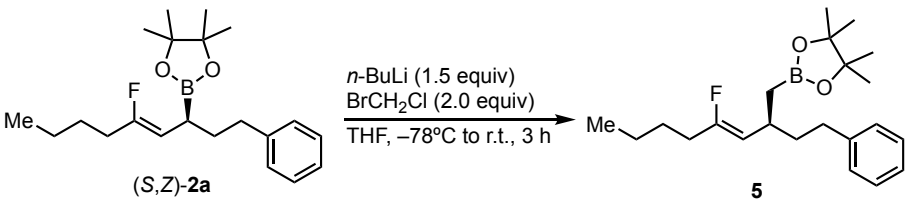
The reaction was conducted with for 1 h with 105.1 mg (0.50 mmol) of (*Z*)-**1p.** The product (*S,Z*)-**2p** was obtained in 88% yield (140.4 mg) with 97.5:2.5 er. The stereoselectivity of (*S,Z*)-**2p** was determined by GC analysis (*Z/E* = >98/2).

$^{1}$H NMR (392 MHz, $CDCl_3$, δ): 0.88 (t, *J* = 4.9 Hz, 3H), 1.26 (s, 12H), 1.23–1.39 (m, 4H), 1.41–1.66 (m, 2H), 2.28–2.38 (m, 1H), 5.40 (dd, *J* = 10.0, 37.4 Hz, 1H), 7.23–7.35 (m, 3H), 7.46–7.52 (m, 2H). $^{13}$C NMR (99 MHz, $CDCl_3$, δ): 14.0 (*C*$H_3$), 20.8 (br, B–*C*H), 22.6 (*C*$H_2$), 24.6 (*C*$H_3$), 30.8 (*C*$H_2$), 31.4 (*C*$H_2$), 83.2 (*C*), 107.6 (d, *J* = 18.2 Hz, *C*H), 123.7 (d, *J* = 6.7 Hz, *C*H), 127.9 (*C*H), 128.2 (*C*H), 156.0 (d, *J* = 245.2 Hz, *C*). $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –121.4 (d, *J* = 45.9 Hz, 1F). HRMS–EI

(*m*/*z*): $[M]^+$ calcd for $C_{19}H_{28}O_2BF$, 318.2170; found, 318.2167. $[\alpha]_D^{20.8}$ –0.8 (*c* 1.21, $CHCl_3$). The er value was determined by HPLC analysis of the corresponding alcohol after oxidation of the boryl group. Daicel CHIRALPAK® IBN-3, 2-PrOH/Hexane = 5/95, 0.5 mL/min, 40°C, retention time: 29.51 min [(*Z*)-alcohol major enantiomer], 16.22 min [(*Z*)-alcohol minor enantiomer].

## Derivatization of γ-Monofluoroallylboronates

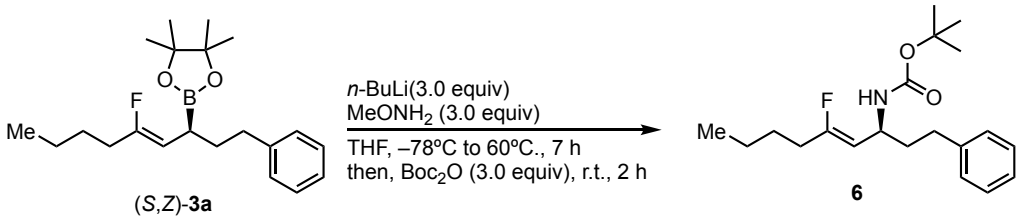
### Experimental Procedure of Homologation of (*S,Z*)-2a.




The homologation was performed according to the literature procedure.[12] In an oven-dried reaction vial, (*S,Z*)-**2a** (34.6 mg, 0.10 mmol) and bromochloromethane (13.4 μL, 0.20 mmol) were dissolved in dry THF (600 μL) in nitrogen atmosphere. After the mixture was cooled to –78 °C, a solution of *n*-BuLi in hexane (1.6 M, 94 μL, 0.15 mmol) was added dropwise. The mixture was stirred at room temperature for 3 h. 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 flash column chromatography ($SiO_2$, $Et_2O$/hexane, 0:100–10:90) to give the corresponding **5** (32.5 mg, 0.090 mmol, 90%) as a colorless oil with 97:3 e.r. The stereoselectivity of **5** was determined by GC analysis (*Z*/*E* = 95/5).

$^1$H NMR (392 MHz, $CDCl_3$, δ): 0.75–0.96 (m, 5H), 1.22 (s, 12H), 1.29–1.40 (m, 2H), 1.41–1.53 (m, 3H), 1.64–1.76 (m, 1H), 2.08–2.20 (m, 2H), 2.46–2.66 (m, 2H), 2.72–2.84 (m, 1H), 4.36 (dd, *J* = 10.1, 38.2 Hz, 1H), 7.11–7.18 (m, 3H), 7.21–7.28 (m, 2H). $^{13}$C NMR (99 MHz, $CDCl_3$, δ): 13.8 (*C*$H_3$), 18.7 (br, B–*C*$H_2$), 22.0 (*C*$H_2$), 24.7 (*C*$H_3$), 24.8 (*C*$H_3$), 28.5 (*C*$H_2$), 30.4 (d, *J* = 3.8 Hz, *C*H), 31.7 (d, *J* = 28.3 Hz, *C*$H_2$), 34.0 (*C*$H_2$), 40.1 (*C*$H_2$), 82.9 (*C*), 110.6 (d, *J* = 15.6 Hz, *C*H), 125.5 (*C*H), 128.2 (*C*H), 128.4 (*C*H), 142.9 (*C*), 158.9 (d, *J* = 254.5 Hz, *C*). $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –90.8 (q, *J* = 22.7 Hz, 1F), –109.2 (dt, *J* = 20.8 Hz, 1F). HRMS-ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{22}H_{34}BFO_2Na$, 383.2532; found, 383.2530. $[\alpha]_D^{18.9}$ +0.66 (*c* 1.00, $CHCl_3$). The er value was determined by HPLC analysis of the corresponding alcohol after oxidation of the boryl group. Daicel CHIRALPAK® IC-3, 2-PrOH/Hexane = 2/98, 0.5 mL/min, 40°C, retention time: 42.91 min [(*Z*)-alcohol major enantiomer], 30.85 min [(*Z*)-alcohol minor enantiomer], 26.29 min [(*E*)-alcohol major enantiomer], and 33.97 min [(*E*)-alcohol minor enantiomer].

**Experimental Procedure of Amination of (*S,Z*)-2a.**

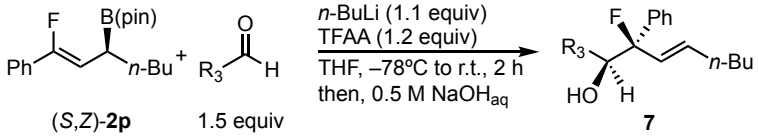



The amination was performed according to the literature procedure.[13] In an oven-dried reaction vial, $MeONH_2$ (0.5 M in THF, 600 μL, 0.30 mmol) was dissolved in THF (200 μL). After the mixture was cooled to –78 °C, a solution of *n*-BuLi in hexane (1.6 M, 188 μL, 0.30 mmol) was added dropwise. Then the boronate (34.6 mg, 0.10 mmol) in THF (240 μL) was added dropwise to the solution and stirred at 60 ºC. After 7 h, $(Boc)_2O$ was added to the reaction mixture and stirred for 2 h at room temperature. The mixture was then quenched by addition of $H_2O$ and extracted three times with $Et_2O$. The combined organic layer was dried over $MgSO_4$ followed by filtration. The crude material was purified by flash column chromatography ($SiO_2$, EtOAc/hexane, 0:100–10:90) to give the corresponding **6** (20.9 mg, 0.060 mmol, 62%) as a colorless oil with 97.5:2.5 er. The stereoselectivity of **6** was determined by GC analysis (*Z*/*E* = >98/2). 1H and $^{13}C$ NMR spectra contain conformational isomers, which is caused by the restricted C–N bond rotation around the carbamate group.

$^1H$ NMR (392 MHz, $CDCl_3$, δ): 0.91 (t, *J* = 7.1 Hz, 3H), 1.29–1.41 (m, 2H), 1.44 (s, 9H), 1.45–1.52 (m, 2H), 1.71–1.83 (m, 1H), 1.86–1.97 (m, 1H), 2.15 (dt, *J* = 7.3, 12.5 Hz, 2H), 2.63 (ddd, *J* = 2.8, 6.7, 9.5 Hz, 2H), 4.36–4.61 (m, 3H), 7.13–7.19 (m, 3H), 7.23–7.28 (m, 2H). $^{13}C$ NMR (99 MHz, $CDCl_3$, δ): 13.8 (*C*$H_3$), 21.9 (*C*$H_2$), 28.1 (*C*$H_2$), 28.4 (*C*$H_3$), 29.7 (*C*), 31.5 (d, *J* = 3.8 Hz, *C*H), 31.7 (d, *J* = 26.9 Hz, *C*$H_2$), 32.3 (*C*$H_2$), 32.3 (*C*$H_2$), 37.7 (*C*$H_2$), 46.3 (*C*H), 83.7 (*C*), 106.2 (*C*H), 125.8 (*C*H), 128.3 (*C*H), 141.7 (*C*), 155.1 (*C*). $^{19}F$ NMR (373 MHz, $CDCl_3$, δ): –104.2 (s, 1F). HRMS-ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{20}H_{30}NFO_2Na$, 358.2153; found, 358.2153. $[\alpha]_D^{18.1}$ +0.14 (*c* 1.58, $CHCl_3$). The er value was determined by HPLC analysis of the corresponding alcohol after oxidation of the boryl group. Daicel CHIRALPAK® IC-3, 2-PrOH/Hexane = 4/96, 0.5 mL/min, 40°C, retention time: 24.21 min [major enantiomer], 13.81 min [minor enantiomer].

## Allylation of Aldehyde with γ-Monofluoroallylboronates

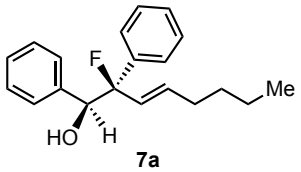
**Experimental procedures of allylation reaction between (*S,Z*)-2p and aldehyde.[14]**




(*S,Z*)-**2p** 1.5 equiv **7**

In an oven-dried reaction vial, a solution of γ-monofluoroallylboronate (*S,Z*)-**2p** (31.8 mg, 0.10 mmol) in THF (1.0 mL) was treated with *n*-BuLi in hexane (1.6 M, 70.6 μL, 0.113 mmol) at –78 °C and the solution was stirred for 15 min. Trifluoroacetic anhydride (17 μL, 0.12 mmol) was added dropwise to the mixture and the reaction was stirred for a further 30 min at –78 °C. Aldehyde (0.15 mmol) was then added at –78 °C and the mixture was stirred for 2 h at –78 ºC, then allowed to slowly warm up to room temperature. After 2 h, the reaction was quenched by addition of 0.5 M aqueous NaOH solution and extracted three times with $Et_2O$. The combined organic layer was dried over $Na_2SO_4$ followed by filtration. The crude material was purified by flash column chromatography ($SiO_2$, $Et_2O$/hexane, 0:100–5:95) or pentane wash of the crude solid material to give the corresponding monofluoro compounds. The products were unstable in $CHCl_3$.

**(1*S*,2*R*,*E*)-2-fluoro-1,2-diphenyloct-3-en-1-ol (7a).**

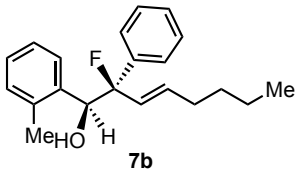



**7a**

The product **7a** was obtained by pentane wash in 54% yield (16.2 mg) with 99:1 er. The stereoselectivity of **7a** was determined by $^1$H NMR analysis (*E*/*Z* = >98/2, dr = >98/2).

$^1$H NMR (396 MHz, $(CD_3)_2CO$, δ): 0.87 (t, *J* = 7.1 Hz, 3H), 1.17–1.39 (m, 4H), 1.98–2.12 (m, 2H), 4.72 (dd, *J* = 2.2, 5.0 Hz, 1H), 5.02 (dd, *J* = 5.0, 14.5 Hz, 1H), 5.63 (dt, *J* = 7.4, 15.0 Hz, 1H), 6.12–6.21 (m, 1H), 7.12–7.43 (m, 10H). $^{13}$C NMR (100 MHz, $(CD_3)_2CO$, δ): 14.3 (*C*H$_3$), 22.9 (*C*H$_2$), 32.0 (*C*H$_2$), 32.8 (*C*H$_2$), 79.5 (d, J = 27.8 Hz, *C*H), 99.2 (d, *J* = 183.0 Hz, *C*), 127.1 (d, *J* = 8.6 Hz, *C*H), 127.9 (*C*H), 128.1 (*C*H), 128.2 (*C*H), 128.5 (*C*H), 129.3 (*C*H), 129.5 (d, *J* = 19.1 Hz, *C*H), 133.1 (d, *J* = 10.5 Hz, *C*H), 141.2 (*C*), 142.6 (d, *J* = 22.0 Hz, *C*). $^{19}$F NMR (373 MHz, $(CD_3)_2CO$, δ): –160.1 (s, 1F). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{20}H_{23}OFNa$, 321.1625; found, 321.1627. $[\alpha]_D^{21.9}$ –0.17 (*c* 1.47, THF). The er value was determined by HPLC analysis. Daicel CHIRALPAK® IF-3, 2-PrOH/Hexane = 1/99, 0.5 mL/min, 40°C, retention time: 44.26 min [major enantiomer], 39.73 min [minor enantiomer].

**(1*S*,2*R*,*E*)-2-fluoro-2-phenyl-1-(*o*-tolyl)oct-3-en-1-ol (7b).**

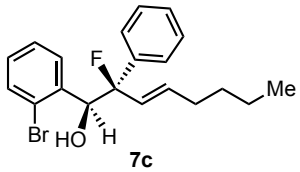



**7b**

The product **7b** was obtained by flash column chromatography in 40% yield (12.4 mg) with 96.5:3.5 er. The stereoselectivity of **7b** was determined by $^1$H NMR analysis (*E*/*Z* = >98/2, d.r. = >98/2). $^1$H NMR (396 MHz, $(CD_3)_2CO$, δ): 0.89 (t, *J* = 7.2 Hz, 3H), 1.20–1.38 (m, 4H), 2.05–2.12 (m, 2H), 2.17 (s, 3H), 4.57 (dd, *J* = 0.8, 4.8 Hz, 1H), 5.28 (dd, *J* = 5.2, 1 1.2 Hz, 1H), 5.61 (dt, *J* = 3.2, 11.2 Hz, 1H), 6.26 (ddt, *J* = 1.5, 15.6, 21.1 Hz, 1H), 6.99–7.05 (m, 1H), 7.08–7.1 (m, 2H), 7.24–7.34 (m, 3H), 7.42–7.46 (m, 3H). $^{13}$C NMR (100 MHz, $(CD_3)_2CO$, δ): 14.2 (*C*H$_3$), 20.0 (d, *J* = 3.8 Hz), 22.9 (*C*H$_2$), 32.0 (*C*H$_2$), 32.9 (*C*H$_2$), 74.9 (d, *J* = 29.2 Hz, *C*H), 99.6 (d, *J* = 178.2 Hz, *C*), 125.6 (*C*H), 127.1 (d, *J* = 8.4 Hz, *C*H), 128.0 (*C*H), 128.3 (*C*H), 128.5 (*C*H), 129.0 (d, *J* = 22.7 Hz, *C*H), 129.8 (*C*H), 130.2 (*C*H), 132.7 (d, *J* = 11.4 Hz, *C*H), 137.1 (*C*), 139.6 (C), 143.3 (d, *J* = 22.0 Hz, *C*). $^{19}$F NMR (373 MHz, $(CD_3)_2CO$, δ): –159.9 (s, 1F). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{21}H_{25}OFNa$, 335.1782; found, 335.1791. $[\alpha]_D^{21.4}$ +2.1 (*c* 1.24, THF). The ee value was determined by HPLC analysis. Daicel CHIRALPAK® IF-3, 2-PrOH/Hexane = 1/99, 0.5 mL/min, 40°C, retention time: 28.38 min [major

enantiomer], 33.68 min [minor enantiomer].

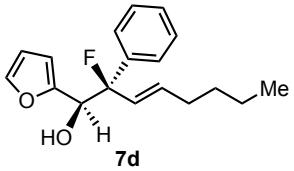
**(1*S*,2*R*,*E*)-1-(2-bromophenyl)-2-fluoro-2-phenyloct-3-en-1-ol (7c).**




**7c**

The product **7c** was obtained by flash column chromatography in 58% yield (21.7 mg) with 97.5:2.5 er. The stereoselectivity of **7c** was determined by $^{1}$H NMR analysis (*E*/*Z* = >98/2, d.r. = >98/2). $^{1}$H NMR (399 MHz, $(CD_3)_2CO$, δ): 0.89 (t, *J* = 7.2 Hz, 3H), 1.24–1.42 (m, 4H), 2.09–2.17 (m, 2H), 5.01 (d, *J* = 5.2 Hz, 1H), 5.52 (dd, *J* = 5.2, 9.2 Hz, 1H), 5.59 (dt, *J* = 7.0, 15.7 Hz, 1H), 6.30 (ddt, *J* = 1.5, 15.7, 20.9 Hz, 1H), 7.17 (td, *J* =1.6, 7.6 Hz, 1H), 7.25–7.37 (m, 4H), 7.46–7.59 (m, 4H). $^{13}$C NMR (100 MHz, $(CD_3)_2CO$, δ): 14.3 (*C*$H_3$), 23.0 (*C*$H_2$), 32.0 (*C*$H_2$), 32.9 (*C*$H_2$), 77.3 (d, *J* = 28.8 Hz, *C*H), 99.1 (d, *J* = 183.0 Hz, *C*), 125.1 (*C*), 127.2 (d, *J* = 8.6 Hz, *C*H), 127.5 (*C*H), 128.3 (d, *J* = 18.2 Hz, *C*H), 128.5 (*C*H), 128.6 (*C*H), 130.1 (*C*H), 131.9 (*C*H), 132.8 (*C*H), 133.2 (d, *J* = 11.5 Hz, *C*H), 140.7 (*C*), 143.31 (d, *J* = 23.0 Hz, *C*). $^{19}$F NMR (373 MHz, $(CD_3)_2CO$, δ): –158.9 (s, 1F). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{20}H_{22}OBrFNa$, 399.0730; found, 399.0734. $[\alpha]_D^{21.8}$ +3.2 (*c* 1.58, THF). The er value was determined by HPLC analysis. Daicel CHIRALPAK® IF-3, 2-PrOH/Hexane = 1/99, 0.5 mL/min, 40°C, retention time: 26.81 min [major enantiomer], 31.59 min [minor enantiomer].

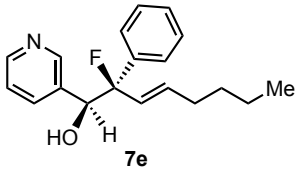
**(1*S*,2*R*,*E*)-2-fluoro-1-(furan-2-yl)-2-phenyloct-3-en-1-ol (7d).**




**7d**

The product **7e** was obtained by flash column chromatography in 60% yield (17.4 mg) with 97.5:2.5 er. The stereoselectivity of **7e** was determined by $^1$H NMR analysis (*E*/*Z* = >98/2, d.r. = >98/2). $^1$H NMR (396 MHz, $(CD_3)_2CO$, δ): 0.88 (t, *J* = 7.3 Hz, 3H), 1.24–1.41 (m, 4H), 2.08–2.15 (m, 2H), 4.80 (d, *J* = 6.3 Hz, 1H), 5.03 (dd, *J* = 6.3, 15.4 Hz, 1H), 5.71 (dtd, *J* = 1.6, 6.9, 15.6 Hz, 1H), 6.13–6.22 (m, 2H), 6.29 (dd, *J* =1.8, 3.2 Hz, 1H), 7.03–7.35 (m, 3H), 7.36–7.43 (m, 3H). $^{13}$C NMR (100 MHz, $(CD_3)_2CO$, δ): 14.2 (*C*H$_3$), 22.8 (*C*H$_2$), 31.9 (*C*H$_2$), 32.8 (*C*H$_2$), 73.9 (d, *J* = 28.7 Hz, *C*H), 98.9 (d, *J* = 182.0 Hz, *C*), 108.9 (*C*H$_2$), 110.9 (*C*H), 126.7 (d, *J* = 9.6 Hz, *C*H), 128.3 (*C*H), 128.5 (*C*H), 129.7 (d, *J* = 18.2 Hz, *C*H), 133.5 (d, *J* = 10.5 Hz, *C*H), 142.1 (d, *J* = 23.0 Hz, *C*), 142.3 (*C*H), 154.8 (*C*). $^{19}$F NMR (373 MHz, $(CD_3)_2CO$, δ): –160.0 (s, 1F). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{18}H_{21}O_2FNa$, 311.1418; found, 311.1421. $[\alpha]_D^{21.8}$ +1.3 (*c* 1.76, THF). The er value was determined by HPLC analysis. Daicel CHIRALPAK® IF-3, 2-PrOH/Hexane = 2/98, 0.5 mL/min, 40°C, retention time: 44.69 min [major enantiomer], 38.80 min [minor enantiomer].

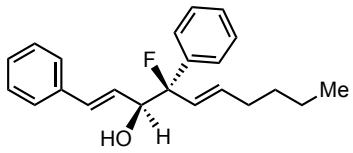
**(1*S*,2*R*,*E*)-2-fluoro-2-phenyl-1-(pyridin-3-yl)oct-3-en-1-ol [7e].**




**7e**

The product **7e** was obtained by flash column chromatography in 56% yield (16.6 mg) with 97:3 er. The stereoselectivity of **7e** was determined by $^1$H NMR analysis (*E*/*Z* = >98/2, d.r. = 93/7).
$^1$H NMR (401 MHz, $(CD_3)_2CO$, δ): 0.87 (t, *J* = 7.2 Hz, 3H), 1.20–1.43 (m, 4H), 2.07–2.13 (m, 2H), 5.00–5.14 (m, 2H), 5.64 (dt, *J* = 7.4, 15.1 Hz, 1H), 6.14–6.26 (m, 1H), 7.18–7.24 (m, 1H), 7.25–7.36 (m, 3H), 7.37–7.42 (m, 2H), 7.63 (d, *J* = 8.4 Hz, 1H), 8.37–8.42 (m, 2H). $^{13}$C NMR (100 MHz, $(CD_3)_2CO$, δ): 14.2 (*C*H$_3$), 22.8 (*C*H$_2$), 31.9 (*C*H$_2$), 32.8 (*C*H$_2$), 77.4 (d, *J* = 27.8 Hz, *C*H), 99.1 (d, *J* = 183.0 Hz, *C*), 123.2 (*C*H), 126.9 (d, *J* = 8.8 Hz, *C*H), 128.5 (*C*H), 128.7 (*C*H), 129.0 (*C*H), 133.7 (d, *J* = 11.5 Hz, *C*H), 136.4 (*C*H), 136.6 (*C*), 142.3 (d, *J* = 22.1 Hz, *C*), 149.4 (*C*H), 150.5 (*C*H). $^{19}$F NMR (373 MHz, $(CD_3)_2CO$, δ): –161.3 (s, 1F). HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{19}H_{23}ONF$, 300.1758; found, 300.1767. $[\alpha]_D^{21.3}$ +0.14 (*c* 1.66, THF). The er value was determined by HPLC analysis. Daicel CHIRALPAK® IF-3, 2-PrOH/Hexane = 1/99, 0.5 mL/min, 40°C, retention time: 43.49 min [major enantiomer], 36.49 min [minor enantiomer].

**(1*E*,3*S*,4*R*,5*E*)-4-fluoro-1,4-diphenyldeca-1,5-dien-3-ol [7f].**

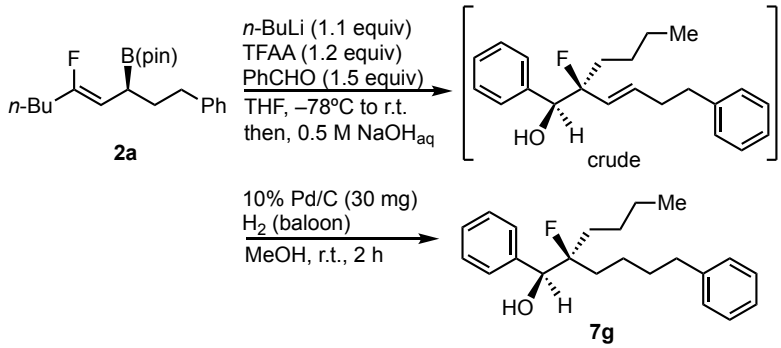



**7f**

The product **7f** was obtained by pentane wash in 33% yield (10.7 mg) with >99:1 er. The stereoselectivity of **7f** was determined by $^1$H NMR analysis (*E*/*Z* = >98/2, d.r. = >98/2).

$^1$H NMR (396 MHz, $(CD_3)_2CO$, δ): 0. 86 (t, *J* = 7.1 Hz, 3H), 1.21–1.40 (m, 4H), 2.06–2.16 (m, 2H), 4.50–4.49 (m, 1H), 4.61 (dt, *J* = 6.3, 13.0 Hz, 1H), 5.79 (dt, *J* =7.4, 15.0 Hz, 1H), 6.13–6.22 (m, 1H), 6.28 (dd, *J* = 6.0, 16.0 Hz, 1H), 6.62 (d, *J* = 15.8 Hz, 1H), 7.20–7.38 (m, 8H), 7.48–7.50 (m, 2H). $^{13}$C NMR (100 MHz, $(CD_3)_2CO$, δ): 14.2 (*C*H$_3$), 22.9 (*C*H$_2$), 32.1 (*C*H$_2$), 32.9 (*C*H$_2$), 78.3 (d, *J* = 28.8 Hz, *C*H), 99.3 (d, *J* = 180.1 Hz, *C*), 126.9 (d, *J* = 9.6 Hz, *C*H), 127.3 (*C*H), 128.3 (d, *J* = 4.8 Hz, *C*H), 128.4 (*C*H), 128.7 (*C*H), 128.9 (d, *J* = 3.8 Hz, *C*H), 129.5 (*C*H), 129.9 (d, *J* = 18.2 Hz, *C*H), 132.7 (*C*H), 133.5 (d, *J* = 10.5 Hz, *C*H), 138.1 (*C*), 142.4 (d, *J* = 22.0 Hz, *C*). $^{19}$F NMR (373 MHz, $(CD_3)_2CO$, δ): –158.8 (s, 1F). HRMS–EI (*m*/*z*): $[M+Na]^+$ calcd for $C_{22}H_{25}OFNa$, 347.1782; found, 347.1787. $[\alpha]_D^{20.8}$ –11.2 (*c* 1.0, THF). The er value was determined by HPLC analysis. Daicel CHIRALPAK® IF-3, 2-PrOH/Hexane = 2/98, 0.5 mL/min, 40°C, retention time: 35.08 min [major enantiomer], 45.09 min [minor enantiomer].

**Allylation reaction between 2a and benzaldehyde followed by $H_2$ hydrogenation with Pd/C.**

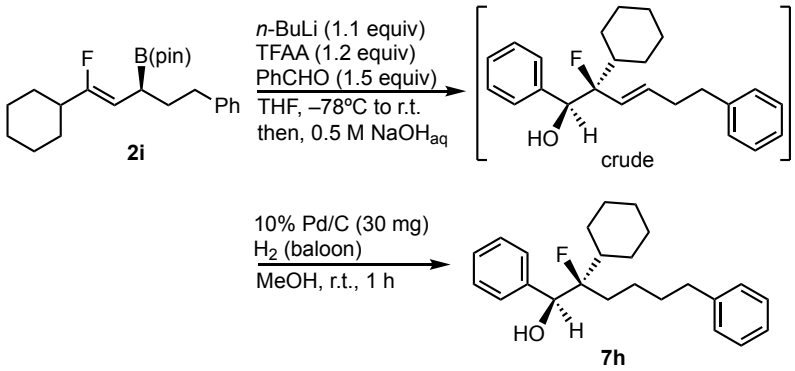



The reaction was conducted with 34.6 mg (0.10 mmol) of **2a**. The title compound was used in the subsequent hydrogenation without further purification. In a reaction vial, 10% Pd/C (30 mg) was dissolved in MeOH (1.0 mL). The crude material of the allylation reaction in MeOH (0.5 mL) was then added to this solution. After stirred for 2 h at room temperature under $H_2$ atmosphere ($H_2$ baloon), the reaction mixture was filtered through a Celite pad and concentrated under reduced pressure. The crude material was purified by flash column chromatography ($SiO_2$, $Et_2O$/hexane, 0:100–10:90). The product **7g** was obtained in 30% yield (10.0 mg) with 98:2 er. The stereoselectivity of **7f** was determined by $^1$H NMR analysis (d.r. = >98/2).

$^1$H NMR (401 MHz, $(CD_3)_2CO$, δ): 0.87 (t, *J* = 7.2 Hz, 3H), 1.21–1.91 (m, 12H), 2.61 (t, *J* = 7.6

Hz, 2H), 4.54 (d, $J$ = 5.2 Hz, 1H), 4.73–4.78 (m, 1H), 7.14–7.42 (m, 10H). $^{13}$C NMR (100 MHz, $(CD_3)_2CO$, δ): 14.4 (*C*H$_3$), 23.6 (d, $J$ = 6.7 Hz, *C*H$_2$), 23.9 (*C*H$_2$), 25.9 (d, $J$ = 4.8 Hz, *C*H$_2$), 32.9 (*C*H$_2$), 33.5 (d, $J$ = 22.9 Hz, *C*H$_2$), 34.4 (d, $J$ = 22.1 Hz, *C*H$_2$), 36.4 (*C*H$_2$), 76.5 (d, $J$ = 24.9 Hz, *C*H), 100.3 (d, $J$ = 177.2 Hz, *C*), 126.5 (*C*H), 128.1 (*C*H), 128.4 (*C*H), 128.9 (*C*H), 129.1 (*C*H), 129.3 (*C*H), 142.3 (*C*), 143.5 (*C*). $^{19}$F NMR (373 MHz, $(CD_3)_2CO$, δ): –161.9 (s, 1F). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{22}H_{29}OFNa$, 351.2095; found, 351.2099. $[\alpha]_D^{21.6}$ +0.99 (*c* 1.00, THF). The er value was determined by HPLC analysis. Daicel CHIRALPAK® IBN-3, 2-PrOH/Hexane = 1.5/98.5, 0.5 mL/min, 40°C, retention time: 34.22 min [major enantiomer], 25.05 min [minor enantiomer].

**Allylation reaction between 2i and benzaldehyde followed by $H_2$ hydrogenation with Pd/C.**

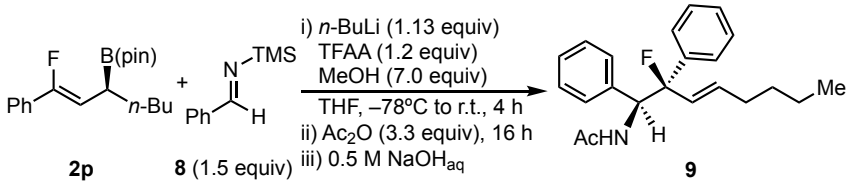



The reaction was conducted with 37.2 mg (0.10 mmol) of **2i**. The title compound was submitted to the subsequent hydrogenation without further purification. In a reaction vial, 10% Pd/C (30 mg) was dissolved in MeOH (1.0 mL). The crude material of the allylation reaction in MeOH (0.5 mL) was then added to this solution. After stirred for 1 h at room temperature under $H_2$ atmosphere ($H_2$ baloon), the reaction mixture was filtered through a Celite pad and concentrated under reduced pressure. The crude material was purified by flash column chromatography ($SiO_2$, $Et_2O$/hexane, 0:100–6:94). The product **7h** was obtained in 53% yield (18.9 mg) with 97:3 er. The stereoselectivity of **7f** was determined by $^1$H NMR analysis (d.r. = 92/8).

$^1$H NMR (392 MHz, $CDCl_3$, δ): 1.02–1.88 (m, 17H), 2.02 (d, $J$ = 3.9 Hz, 1H), 2.60 (t, $J$ = 7.4 Hz, 2H), 4.93 (dd, $J$ = 4.3, 13.3 Hz, 1H), 7.14–7.41 (m, 10H). $^{13}$C NMR (99 MHz, $CDCl_3$, δ): 22.9 (d, $J$ = 8.0 Hz, *C*H$_2$), 26.4 (*C*H$_2$), 26.5 (*C*H$_2$), 26.7 (*C*H$_2$), 26.5 (d, $J$ = 8.5 Hz, *C*H$_2$), 27.4 (d, $J$ = 5.2 Hz, *C*H$_2$), 31.3 (d, $J$ = 23.2 Hz, *C*H$_2$), 32.1 (*C*H$_2$), 35.7 (*C*H$_2$), 42.1 (d, $J$ = 21.3 Hz, *C*H), 100.6 (d, $J$ = 175.5 Hz, *C*), 125.6 (*C*H), 127.4 (d, $J$ = 1.9 Hz, *C*H), 127.7 (*C*H), 128.0 (*C*H), 128.2 (*C*H), 128.3 (*C*H), 140.4 (*C*), 142.5 (*C*). $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –164.5 (d, $J$ = 33.9 Hz, 1F). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{24}H_{31}OFNa$, 377.2251; found, 377.2255. $[\alpha]_D^{19.7}$ +1.64 (*c* 1.55, $CHCl_3$). The er value was determined by HPLC analysis. Daicel CHIRALPAK® IBN-3, 2-PrOH/Hexane = 1.5/98.5, 0.5 mL/min, 40°C, retention time: 46.95 min [*syn*-**7h** major enantiomer], 29.58 min [*syn*-**7h** minor enantiomer], 29.58 min [*anti*-**7h** major enantiomer], and 27.17 min [*anti*-**7h** minor enantiomer].

## Allylation of Aldimine with γ-Monofluoroallylboronates

**Experimental procedures of allylation reaction between 2p and aldimine.[8]**




**2p** **8** (1.5 equiv) **9**

In an oven-dried reaction vial, a solution of γ-monofluoroallylboronate **2p** (31.8 mg, 0.10 mmol) in THF (1.0 mL) was treated with *n*-BuLi in hexane (1.6 M, 70.6 μL, 0.113 mmol) at –78 °C and the solution was stirred for 15 min. Trifluoroacetic anhydride (16.9 μL, 0.12 mmol) was added dropwise to the mixture and the reaction was stirred for a further 30 min at –78 °C. *N*-Trimethylsilyl benzaldimine (18.4 μL, 0.15 mmol) and MeOH (30 μL, 0.74 mmol) was then added at –78 °C and the mixture was stirred for 1 h at –78 ºC, then allowed to slowly warm up to room temperature. After 3 h, $Ac_2O$ (34 μL, 0.33 mmol) was added to the reaction mixture and stirred at room temperature. After 16 h, the reaction was quenched by addition of 0.5 M aqueous NaOH solution and extracted three times with $Et_2O$. The combined organic layer was dried over $Na_2SO_4$ followed by filtration. The solid crude material was purified by hexane wash. The product **9** was obtained in 59% yield (20.0 mg) with 98:2 er. The stereoselectivity of **9** was determined by $^1$H NMR analysis (*E*/*Z* = >98/2, d.r. = >98/2).

$^1$H NMR (396 MHz, $(CD_3)_2CO$, δ): 0.89 (t, *J* = 6.9 Hz, 3H), 1.25–1.43 (m, 4H), 1.93 (s, 3H), 2.07–2.13 (m, 2H), 5.53 (dd, *J* = 9.5, 30.1 Hz, 1H), 5.77–5.84 (m, 1H), 5.95–6.03 (m, 1H), 7.06–7.24 (m, 10H), 7.83–7.94 (m, 1H). $^{13}$C NMR (100 MHz, $(CD_3)_2CO$, δ): 14.2 (*C*H$_3$), 22.8 (*C*H$_2$), 22.9 (*C*H$_3$), 32.1 (*C*H$_2$), 32.7 (*C*H$_2$), 60.2 (d, *J* = 20.2 Hz, *C*H), 100.8 (d, *J* = 185.9 Hz, C), 125.8 (d, *J* = 9.5 Hz, *C*H), 127.8 (*C*H), 128.0 (*C*H), 128.3 (*C*H), 128.7 (*C*H), 129.9 (*C*H), 131.1 (d, *J* = 19.1 Hz, *C*H), 132.3 (d, *J* = 10.5 Hz, CH), 139.1 (*C*), 142.1 (d, *J* = 22.0 Hz, *C*), 169.3 (*C*). $^{19}$F NMR (373 MHz, $(CD_3)_2CO$, δ): –169.6 (t, *J* = 22.8 Hz, 1F). HRMS–EI (*m*/*z*): $[M+Na]^+$ calcd for $C_{22}H_{26}ONFNa$, 362.1891; found, 362.1900. $[\alpha]_D^{21.0}$ +0.12 (*c* 1.68, THF). The er value was determined by HPLC analysis. Daicel CHIRALPAK® IF-3, 2-PrOH/Hexane = 15/85, 0.5 mL/min, 40°C, retention time: 13.15 min [major enantiomer], 16.64 min [minor enantiomer].

**Single Crystal X-ray Structural Analysis**

The absolute configuration of the products were determined based on X-ray crystallographic analysis of the products **2i**, **2p**, **7a** and **7h**. The absolute configurations of other products were deduced by these products. The details were summarized in Figure S1–S4 and Table S1–S4.

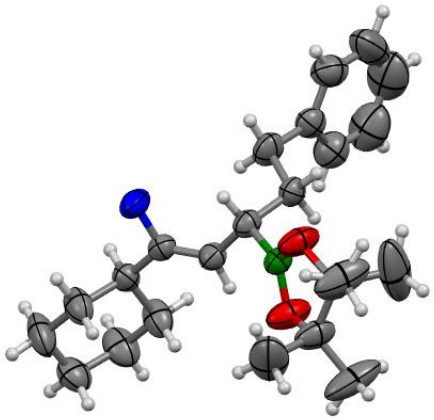


**Figure S1.** Molecular structure of (*S,Z*)-**2i**. Thermal ellipsoids set at 50% probability.

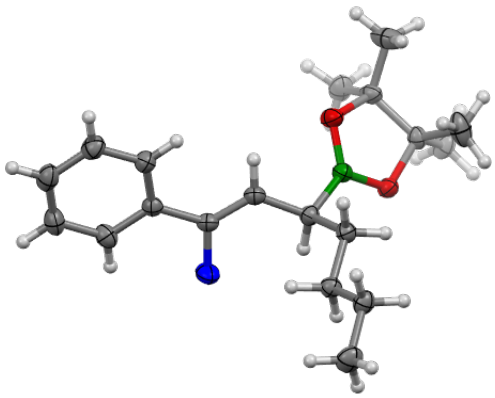


**Figure S2.** Molecular structure of (*S,Z*)-**2p**. Thermal ellipsoids set at 50% probability.

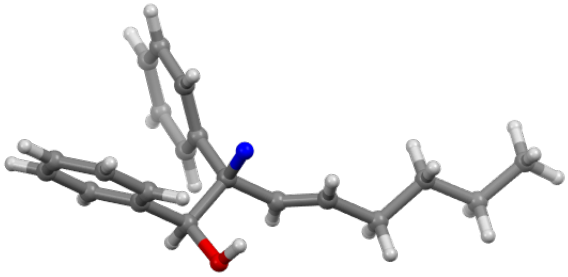


**Figure S3.** Molecular structure of (1*S*,2*R*,*E*)-**7a**.

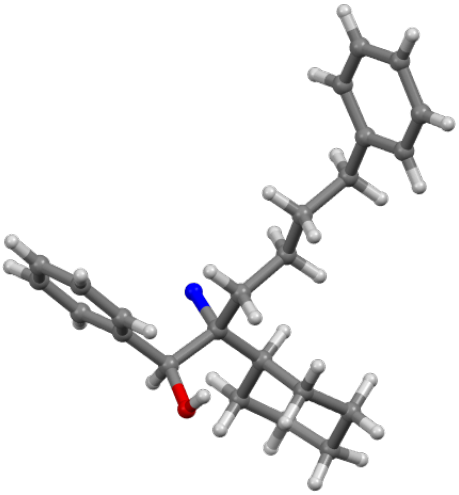


**Figure S4.** Molecular structure of (1*S*,2*R*)-**7h**.

**Table S1.** Summary of X-ray crystallographic data for (*S,Z*)-**2i.**

| | |
|---|---|
| CCDC | 1905700 |
| Empirical formula | $C_{23}H_{34}BFO_2$ |
| Formula weight | 372.31 |
| Temperature/K | 243 |
| Crystal system | monoclinic |
| Space group | $P2_1$ |
| $a$ / Å | 6.51580(10) |
| $b$ / Å | 20.1138(3) |
| $c$ / Å | 8.74810(10) |
| $\alpha$/° | 90 |
| $\beta$/° | 99.239(2) |
| $\gamma$/° | 90 |
| Volume/Å$^3$ | 1131.63(3) |
| $Z$ | 2 |
| $\rho_{calc}$ g/cm$^3$ | 1.093 |
| $\mu$/mm$^{-1}$ | 0.572 |
| F(000) | 404.0 |
| Crystal size/mm$^3$ | 0.38×0.26×0.21 |
| Radiation | CuKα ($\lambda$ = 1.54184) |
| 2$\theta$ range for data collection/° | 8.792 to 147.57 |
| Index ranges | $-7 \leqq h \leqq 7$, $-24 \leqq k \leqq 24$, $-10 \leqq l \leqq 10$ |
| Reflections collected | 11342 |
| Independent reflections | 4405 [$R_{int}$ = 0.0233, $R_{sigma}$ = 0.0251] |
| Data/restraints/parameters | 4405/1/248 |
| Goodness-of-fit on F$^2$ | 1.072 |
| Final $R$ indexes [I>=2σ (I)] | $R_1$ = 0.0581, $wR_2$ = 0.1715 |
| Final $R$ indexes [all data] | $R_1$ = 0.0611, $wR_2$ = 0.1735 |
| Largest diff. peak/hole / e Å$^{-3}$ | 0.33/–0.18 |
| Flack parameter | 0.06(8) |

**Table S2.** Summary of X-ray crystallographic data for (*S,Z*)-**2p.**

| | |
|---|---|
| CCDC | 1905696 |
| Empirical formula | $C_{19}H_{28}BFO_2$ |
| Formula weight | 318.22 |
| Temperature/K | 123 |
| Crystal system | orthorhombic |
| Space group | $P2_12_12_1$ |
| $a$ / Å | 9.29320(10) |
| $b$ / Å | 11.89520(10) |
| $c$ / Å | 16.6460(10) |
| $\alpha$/° | 90 |
| $\beta$/° | 90 |
| $\gamma$/° | 90 |
| Volume/Å$^3$ | 1840.12(3) |
| $Z$ | 4 |
| $\rho_{calc}$ g/cm$^3$ | 1.149 |
| $\mu$/mm$^{-1}$ | 0.625 |
| F(000) | 688.0 |
| Crystal size/mm$^3$ | 0.274×0.147×0.1 |
| Radiation | CuKα ($\lambda$ = 1.54184) |
| 2$\theta$ range for data collection/° | 9.138 to 148.066 |
| Index ranges | $-11 \leqq h \leqq 11$, $-14 \leqq k \leqq 14$, $-20 \leqq l \leqq 20$ |
| Reflections collected | 53118 |
| Independent reflections | 3701 [$R_{int}$ = 0.1171, $R_{sigma}$ = 0.0316] |
| Data/restraints/parameters | 3701/0/213 |
| Goodness-of-fit on F$^2$ | 1.099 |
| Final $R$ indexes [I>=2σ (I)] | $R_1$ = 0.0460, $wR_2$ = 0.1165 |
| Final $R$ indexes [all data] | $R_1$ = 0.0486, $wR_2$ = 0.1200 |
| Largest diff. peak/hole / e Å$^{-3}$ | 0.14/–0.28 |
| Flack parameter | –0.05(7) |

**Table S3.** Summary of X-ray crystallographic data for **7a.**

| | |
|---|---|
| CCDC | 1905693 |
| Empirical formula | $C_{20}H_{23}FO$ |
| Formula weight | 298.38 |
| Temperature/K | 123 |
| Crystal system | monoclinic |
| Space group | $P2_1$ |
| $a$ / Å | 16.0231(2) |
| $b$ / Å | 5.46870(10) |
| $c$ / Å | 18.5413(3) |
| $\alpha$/° | 90 |
| $\beta$/° | 92.4760(10) |
| $\gamma$/° | 90 |
| Volume/Å$^3$ | 1623.17(4) |
| $Z$ | 4 |
| $\rho_{calc}$ g/cm$^3$ | 1.221 |
| $\mu$/mm$^{-1}$ | 0.644 |
| F(000) | 640.0 |
| Crystal size/mm$^3$ | 0.342×0.04×0.04 |
| Radiation | CuKα ($\lambda$ = 1.54184) |
| 2$\theta$ range for data collection/° | 4.77 to 140.628 |
| Index ranges | $-17 \leqq h \leqq 19$, $-5 \leqq k \leqq 6$, $-22 \leqq l \leqq 22$ |
| Reflections collected | 55714 |
| Independent reflections | 5650 [$R_{int}$ = 0.01826, $R_{sigma}$ = 0.0531] |
| Data/restraints/parameters | 5650/1/353 |
| Goodness-of-fit on F$^2$ | 1.036 |
| Final $R$ indexes [I>=2σ (I)] | $R_1$ = 0.0598, $wR_2$ = 0.1584 |
| Final $R$ indexes [all data] | $R_1$ = 0.0627, $wR_2$ = 0.1619 |
| Largest diff. peak/hole / e Å$^{-3}$ | 0.50/–0.41 |
| Flack parameter | 0.03(15) |

**Table S4.** Summary of X-ray crystallographic data for **7h.**

| | |
|---|---|
| CCDC | 1905684 |
| Empirical formula | $C_{24}H_{31}FO$ |
| Formula weight | 354.49 |
| Temperature/K | 123 |
| Crystal system | monoclinic |
| Space group | $P2_1$ |
| $a$ / Å | 12.0730(10) |
| $b$ / Å | 5.54330(10) |
| $c$ / Å | 14.6277(2) |
| $\alpha$/° | 90 |
| $\beta$/° | 96.7300(10) |
| $\gamma$/° | 90 |
| Volume/Å$^3$ | 972.26(2) |
| $Z$ | 2 |
| $\rho_{calc}$ g/cm$^3$ | 1.211 |
| $\mu$/mm$^{-1}$ | 0.613 |
| F(000) | 384.0 |
| Crystal size/mm$^3$ | 0.295×0.11×0.06 |
| Radiation | CuKα ($\lambda$ = 1.54184) |
| 2$\theta$ range for data collection/° | 6.084 to 148.214 |
| Index ranges | $-14 \leqq h \leqq 15$, $-6 \leqq k \leqq 6$, $-18 \leqq l \leqq 18$ |
| Reflections collected | 37395 |
| Independent reflections | 3847 [$R_{int}$ = 0.1160, $R_{sigma}$ = 0.0378] |
| Data/restraints/parameters | 3847/1/236 |
| Goodness-of-fit on F$^2$ | 1.065 |
| Final $R$ indexes [I>=2σ (I)] | $R_1$ = 0.0473, $wR_2$ = 0.1284 |
| Final $R$ indexes [all data] | $R_1$ = 0.0501, $wR_2$ = 0.1312 |
| Largest diff. peak/hole / e Å$^{-3}$ | 0.23/–0.22 |
| Flack parameter | 0.03(11) |

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# Chapter2.

# Copper(I)-Catalyzed Boryl Substitution of 1-Trifluoromethyl Allenes

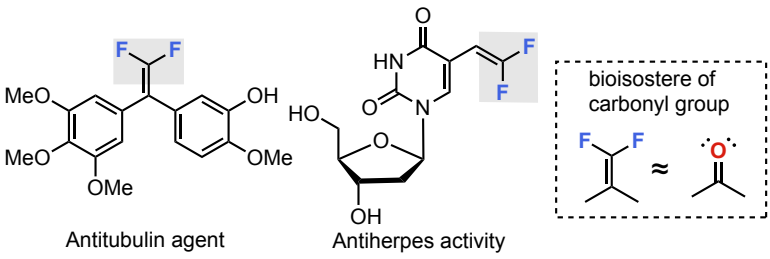
## Abstract

A method to synthesize 3-boryl-1,1-*gem*-difluorodienes via the copper(I)-catalyzed boryl substitution of trifluoromethyl-substituted allenes was developed. The borylated compounds were obtained in up to 91% yield with excellent selectivity. I proposed that the reaction proceeded via γ-selective borylcupration into the trifluoromethyl-substituted allene followed by copper(I)-*β*-fluoro elimination. Subsequent transformations of the borylation product by Suzuki–Miyaura cross-coupling or Diels–Alder reaction provided various compounds bearing a difluoro moiety, which are difficult to synthesize by existing methods.


## Introduction

Organofluorine compounds are used in many applications in various research fields because the introduction of fluorine atom(s) or fluorinated moieties into organic molecules can dramatically alter the reactivity and physical, chemical, and biological properties of target molecules.[1] Among numerous fluorine-containing compounds, the *gem*-difluoroalkenyl moiety, which has been considered isosteric and isopolar to carbonyl groups, is an attractive target. Thus, demand for efficient methods to access compounds with a *gem*-difluoroalkenyl group has increased steadily (Figure 1).[2,3]

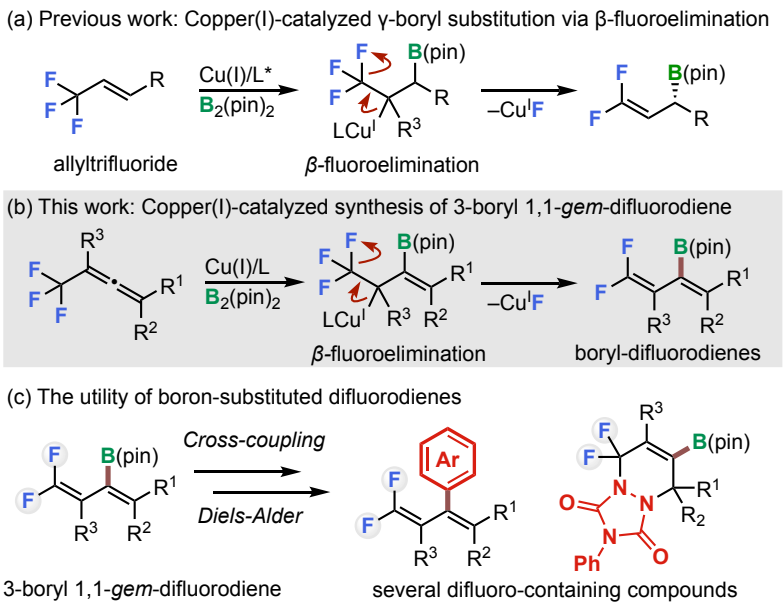
***Figure 1.*** Examples of difluorovinyl-containing bioactive compounds




Fluorine-containing organoboron compounds are attractive synthons that have great potential for the flexible assembly of an array of structurally diverse organofluorine compounds.[2c,4] Recently, several groups have reported the selective syntheses of fluorine-containing organoboron compounds through transition metal-mediated C–F bond activation.[5,6] We previously reported the copper(I)-catalyzed enantioselective borylation reactions of allyltrifluorides and allyldifluorides using bis(pinacolato)diboron.[7] These reactions presumably proceed through the enantioselective borylcupration of alkenes, followed by copper(I)-*β*-fluoro elimination to give *gem*-difluoroallylboronates (Scheme 1a).[8,9] Based on our studies, the author anticipated that 3-boryl-1,1-*gem*-difluorodienes could be efficiently synthesized by the borylation

of 1-trifluoromethyl-substituted allenes through the regioselective borylcupration/copper(I)-*β*-fluoro elimination sequence (Scheme 1b).[9c,10,11] The products would be versatile intermediates to obtain potentially useful *gem*-difluoroalkenyl compounds, which are difficult to obtain by other methods, through cross-coupling reactions with aryl halides. In addition, a Diels–Alder reaction between the product and an electron-deficient alkene would allow the construction of complex structural motifs containing a difluoromethyl moiety (Scheme 1c).

***Scheme 1.*** The summary of this work

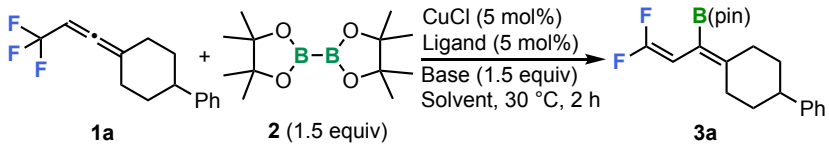



## Result and discussion

The author began by searching for optimal conditions for the transformation of $CF_3$-substituted allene **1a** (Table 1). With CuCl/$PPh_3$ (5 mol%), $B_2(pin)_2$ (**2**), and NaOMe, **3a** was generated from **1a** in 92% yield (Table 1, entry 1). The use of other diphosphine ligands such as Xantphos, dppe, and dppf also deliverd **3a** in high yield (Table 1, entries 2–4). However, the use of an imidazolium salt such as 1,3-dimesitylimidazolium chloride (IMes•HCl) as a precursor of the corresponding *N*-heterocyclic carbene (NHC) ligand led to a substantial decrease in reactivity (Table 1, entry 5). The nature of the bases was also found to have a marked impact on the reactivity (Table 1, entries 6–8). For example, the use of Na(O-*t*-Bu) and K(O-*t*-Bu) resulted in a slight change in reactivity, whereas the use of other bases such as LiOMe led to a considerable decrease in reactivity. These results indicated that the choice of the counter cation of the base is crucial for this reaction. Changing the solvent from THF to 1,3-dimethyl-2-imidazolidinone (DMI) or toluene provided similar results (Table 1, entries 9 and 10). Notably, although the yield is the highest with DMI solvent, the author chose THF as the solvent considering ease of handling. Use

of a catalytic amount of NaOMe resulted in a low yield (27%, Table 1, entry 11). The reaction proceeded without the ligand despite a decreased yield was observed (69%, Table 1, entry 12).

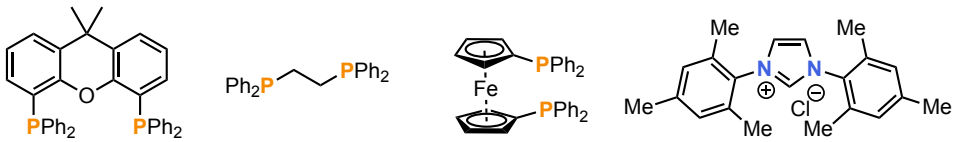
***Table 1.*** Optimization of the reaction conditions[a]




**1a** **2** (1.5 equiv) **3a**

| Entry | Ligand | Base | Solvent | Yield (%)[b] |
|---|---|---|---|---|
| 1 | $PPh_3$ | NaOMe | THF | 92 |
| 2 | Xantphos | NaOMe | THF | 87 |
| 3 | dppe | NaOMe | THF | 89 |
| 4 | dppf | NaOMe | THF | 89 |
| 5 | IMes | NaOMe | THF | trace |
| 6 | $PPh_3$ | Na(O-*t*-Bu) | THF | 92 |
| 7 | $PPh_3$ | K(O-*t*-Bu) | THF | 87 |
| 8 | $PPh_3$ | LiOMe | THF | trace |
| 9 | $PPh_3$ | NaOMe | DMI | 95 |
| 10 | $PPh_3$ | NaOMe | Toluene | 78 |
| 11[c] | $PPh_3$ | NaOMe | THF | 27 |
| 12 | none | NaOMe | THF | 69 |

[a]Conditions: **1** (0.25 mmol), CuCl (0.0125 mmol), ligand (0.0125 mmol), base (0.375 mmol), **2** (0.375 mmol) in THF (500 μL). [b]Determined by $^{19}F$ NMR analysis of the crude mixture with a fluorobenzene as an internal standard. [c]NaOMe (10 mol%) was used as the base.

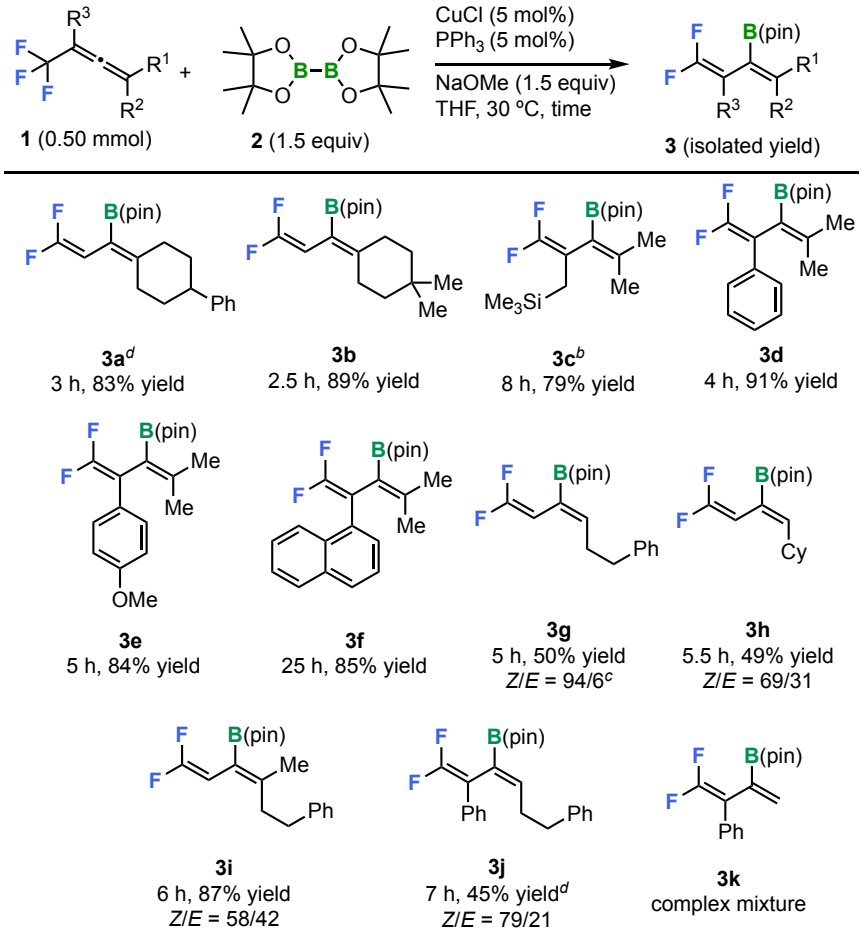



Xantphos dppe dppf IMes·HCl

Next, the optimized conditions were used to evaluate the substrate scope (Table 2). Model substrate **1a** and the similar substrate **1b** were reacted with **2** under the optimized conditions to give the corresponding products in high yield (**3a:** 83%, **3b**: 89%, **3a** contained trace amounts of byproducts). Tetrasubstituted allenes bearing a silyl group (**1c**) or aryl group (**1d**–**1f**) also reacted smoothly to give corresponding multisubstituted *gem*-difluorodienes (**3c**: 79%, **3d**: 91%, **3e**: 84%, and **3f**: 85%). Furthermore, the author conducted the reaction using trifluoromethyl allenes with asymmetric substituents on the C3 carbon atom. The reaction of a substrate with 3-monosubstituted allene **1g** proceeded smoothly with high *Z*/*E* ratio (**3g**: 50%, *Z*/*E* = 94/6).

Although cyclohexyl-substituted product **3h** was obtained with similar reactivity to that of the other substrates, a lower *Z*/*E* ratio was observed (**3h**: 49%, *Z*/*E* = 69/31). In addition, 3,3-disubstituted and 1,3-disubstituted trifluoromethyl allenes were converted to the corresponding products but low to moderate *Z*/*E* ratios were observed (**3i**: 87%, *Z*/*E* = 58/42; **3j**: 45%, *Z*/*E* = 79/21, **3j** contained trace amounts of byproducts). Unfortunately, the reaction of trifluoromethyl-substituted terminal allene **1k** resulted in a complex mixture.

***Table 2.*** Optimization of the reaction conditions[a]

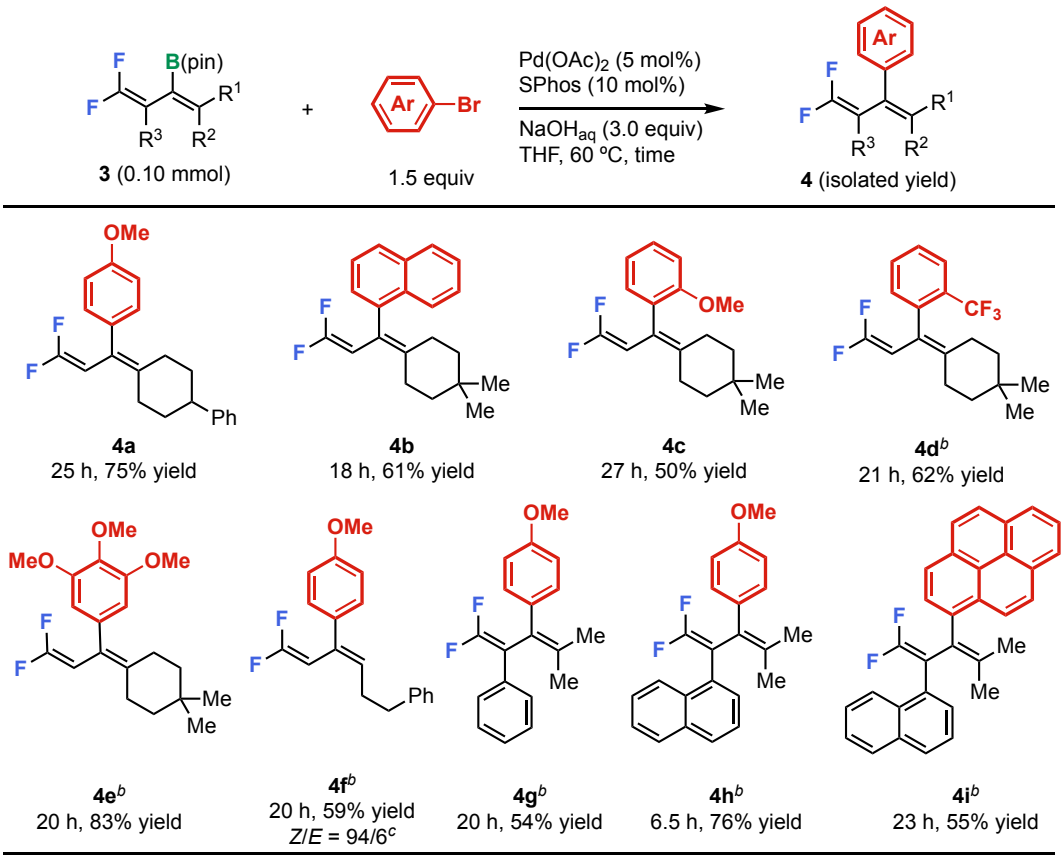



[a]Conditions: **1** (0.50 mmol), CuCl (0.025 mmol), $PPh_3$ (0.025 mmol), NaOMe (0.75 mmol), and **2** (0.75 mmol) in THF (1.0 mL). [b]Conducted on 0.25 mmol scale. [c]Determined by GC and 2D NOESY analyses. [d]Contained a small amount of byproduct.

The author conducted several transformation reactions to demonstrate the utility of the newly synthesized 3-boryl-1,1-*gem*-difluorodienes (Table 3). First, I focused on Suzuki–Miyaura cross-coupling reactions using the boryl substitution products with aryl halides as the coupling partner.[12] This transformation would provide useful routes to synthesize functionalized difluoro

compounds in a stereoretentive manner. The reaction of **3a** with *p*-methoxyphenyl bromide in the presence of $Pd(OAc)_2$/SPhos as a catalyst afforded the corresponding coupling product in high yield (**4a**: 75%). The reaction of **3b** with naphthyl bromide and *o*-methoxy bromide afforded the corresponding difluoro compounds in moderate yield (**4b**: 61%, **4c**: 50%). Other aryl bromides bearing an electron-deficient $CF_3$ or 3,4,5-trimethoxy group were also suitable substrates for this transformation (**4d**: 62%, **4e**: 83%). Furthermore, **4f** was obtained from **3g** and retained a high *Z*/*E* ratio (**4f**: 59%, *Z*/*E* = 94/6). The reaction of **3d** and **3f** with *p*-methoxyphenyl bromide provided interesting π-conjugated difluoroalkenyl compounds **4g** and **4h**, respectively (**4g**: 54%, **4h**: 76%). In addition, π-conjugated **4i** was obtained by reaction with 1-bromopyrene. These π-conjugated difluoroalkenyl compounds are potentially useful building blocks for fluorinated organic materials but are difficult to prepare using existing methods.[13]

***Table 3.*** Optimization of the reaction conditions[a]

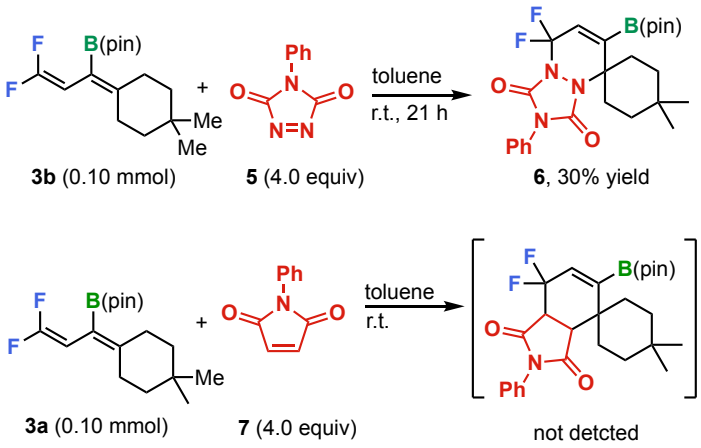



[a]Conditions: **3** (0.10 mmol), ArBr (0.15 mmol), $Pd(OAc)_2$ (0.005 mmol), SPhos (0.010 mmol), and 2.5M $NaOH_{aq}$ (0.30 mmol) in THF (210 μL). [b]ArBr (1.05 equiv) was used. [c]Determined by GC analysis.

Next, we conducted the Diels–Alder reaction of **3b**.[14] As a result, the reaction of **3b** with a highly reactive dienophile **5** afforded difluoro-containing heterocyclic vinyl boronate **6** in 30%

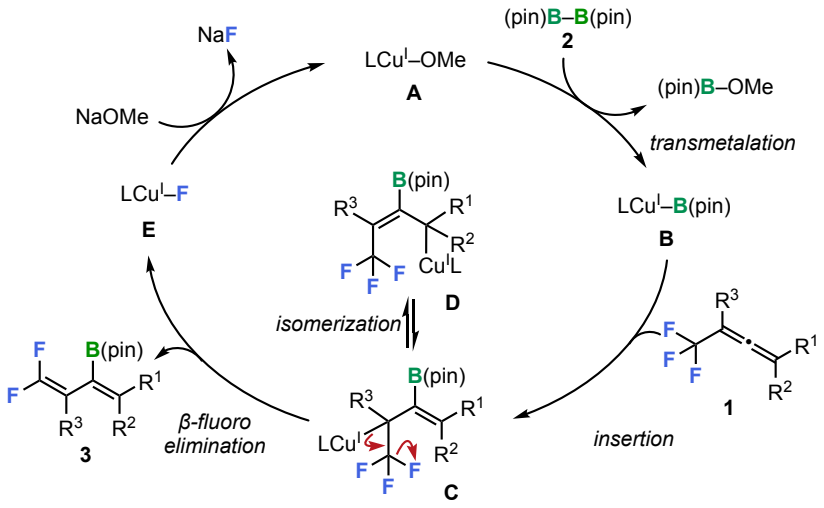
yield (Scheme 2) , despite commonly used dienophiles such as maleic anhydride **7** found to be unreactive toward **3b**, probably due to the effect of fluorine moiety in diene moiety. This derivatization provides a synthetic route to access complex fluorinated compounds.

***Scheme 2.*** Diels-Alder reactions of **3b** with several dienophiles[a]



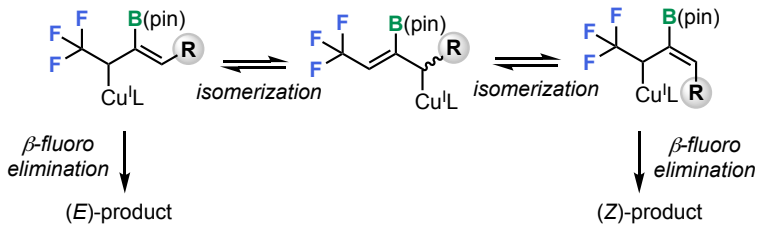

The author propose a possible reaction mechanism for the current copper(I)-catalyzed borylation of trifluoromethyl-substituted allenes, which is shown in Figure 2.[7,9c] The reaction of CuCl with the ligand and NaOMe would result in the formation of copper(I) alkoxide intermediate **A**, which would initially react with diboron **2** to afford the boryl copper(I) intermediate **B**. Then, the C–C double bond of an allene inserts into the Cu–B bond of intermediate **B** to afford σ-allyl copper intermediates **C** and **D.** Subsequent *β*-fluoro elimination of **C** gives 3-boryl *gem*-difluorodiene **3** and a copper(I) fluoride intermediate **E,** which would react with NaOMe to regenerate copper(I) alkoxide intermediate **A** and close the catalytic cycle.

***Figure 2.*** Propsed reaction mechanism of this reaction




The variations in the *Z*/*E* ratios of substrates **3g**–**3j** may be caused by the fast $\eta^1$–$\eta^3$ interconversion from **C** to **D**, in which the equilibrium between **C** and **D** depends on the substituents on the allene (Figure 3). The proposed reason for the complex mixture obtained from the reaction of substrate **3k** would be the difficulty of *β*-fluoro elimination because the less sterically hindered intermediate **D** is more stable than **C**, which traps the reaction.

***Figure 3.*** The details of the *Z*/*E* isomerization




## Conclusion

In summary of this chapter, the author developed a copper(I)-catalyzed boryl substitution reaction of trifluoromethyl-substituted allenes that provides access to novel difluoro compounds. The cross-coupling reactions between the borylation products and aryl bromides provided functionalized difluorodiene derivatives in good yield. Additionally, I obtained a difluoro-containing cyclic vinyl boronate through a Diels–Alder reaction. I believe that the newly synthesized organoboron reagents—3-boryl-1,1-*gem*-difluorodienes—which are difficult to access by previous synthetic methods, will be useful building blocks for the preparation of various organofluorine compounds.

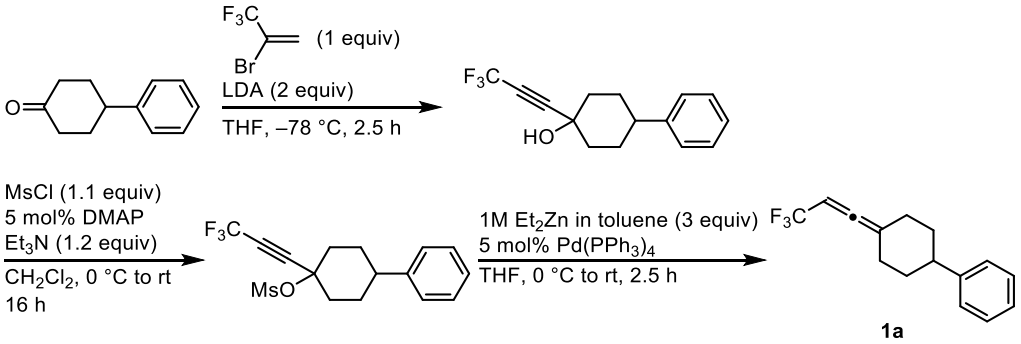
# Experiment

## 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). NMR spectra were recorded on JEOL JNM-ECX400P and JNM-ECS400 spectrometers ($^{1}$H: 392, 396, 400 and 401 MHz, $^{13}$C: 99 and 100 MHz and $^{19}$F: 373 MHz). Tetramethylsilane ($^{1}$H), $CDCl_3$ ($^{13}$C) and fluorobenzene ($^{19}$F, δ –113.60) were employed as the external standards, respectively. Fluorobenzene was used as an internal standard to determine NMR yield. Multiplicity was recorded as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. CuCl (ReagentPlus® grade, 224332-25G, ≥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. 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 $CF_3$-Substituted Allenes

**Preparation of 2-[3,3-difluoro-1-(4-phenylcyclohexylidene)allyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1a).[16,17]**




In a vacuum dried 300 mL two necked round bottomed flask, 1.6 M solution of *n*-BuLi in hexane (25 mL, 40.0 mmol) was added dropwise to a solution of diisopropylamine (5.6 mL, 40.0 mmol) in THF (30 mL) at 0 °C under nitrogen atmosphere. The mixture was stirred for 1 h at that temperature. The lithium diisopropylamine (LDA) mixture was cooled to –78 °C, and 2-bromo-3,3,3-trifluoropropene (2.1 mL, 20.0 mmol) in THF (10 mL) was slowly added at –78 °C. After the solution was stirred for 1 h, 4-phenylcyclohexanone (3.49 g, 20.0 mmol) in THF (10 mL) was added and the mixture was stirred for 2.5 h at that temperature. The reaction mixture was quenched with 1 M HCl (100 mL) at 0 ℃ and extracted with EtOAc three times. The combined organics were washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified by flash silica gel column chromatography ($SiO_2$, EtOAc/hexane, 0:100–11:89). The product was obtained in 67% yield (3.57 g, 13.3 mmol).

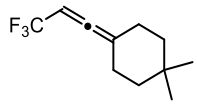
In a vacuum dried 200 mL two necked round bottomed flask, $Et_3N$ (2.2 mL, 16.0 mmol) was added dropwise to a solution of alcohol (3.57 g, 13.3 mmol), methanesulfonyl chloride (1.1 mL, 14.7 mmol), 4-dimethylaminopyridine (81.8 mg, 0.67 mmol) in $CH_2Cl_2$ (53 mL) at 0 °C under nitrogen atmosphere. The solution was stirred for 16 h at room temperature. The reaction mixture was quenched with saturated aqueous $NH_4Cl$ (40 mL) at 0 °C and extracted with $CH_2Cl_2$ three times. The combined organics were washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified by flash silica gel column chromatography ($SiO_2$, EtOAc/hexane, 0:100–15:85). The product was obtained in 61% yield (2.79 g, 8.1 mmol).

In a vacuum dried 300 mL two necked round bottomed flask, $Et_2Zn$ (24.2 mL, 24.2 mmol, 1.0 M in toluene) was added dropwise to a solution of the methanesulfonyl compound (2.79 g, 8.1 mmol) and $Pd(PPh_3)_4$ (468.5 mg, 0.41 mmol) in THF (82 mL) at 0 °C under nitrogen atmosphere. The solution was stirred for 2.5 h at room temperature. The reaction mixture was quenched with

saturated aqueous $NH_4Cl$ (66 mL) at 0 °C, filtered through celite, extracted with EtOAc three times. The combined organics were washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified by flash silica gel column chromatography ($SiO_2$, hexane only). **1a** was obtained in 45% yield (924.5 mg, 3.7 mmol) as a white solid.

$^1$H NMR (392 MHz, $CDCl_3$, δ): 1.64 (dq, $J$ = 3.7, 12.9 Hz, 2H), 2.00–2.09 (m, 2H), 2.28 (tt, $J$ = 4.3, 13.5 Hz, 2H), 2.54 (d, $J$ = 14.1 Hz, 2H), 2.65 (tt, $J$ = 3.9, 12.2 Hz, 1H), 5.32–5.40 (m, 1H), 7.18–7.24 (m, 3H), 7.28–7.34 (m, 2H). $^{13}$C NMR (99 MHz, $CDCl_3$, δ): 30.2 ($C$H$_2$), 34.0 ($C$H$_2$), 43.5 ($C$H), 83.7 (q, $J$ = 39.0 Hz, $C$H), 108.9 ($C$), 123.0 (q, $J$ = 271.6 Hz, $C$), 126.3 ($C$H), 126.7 ($C$H), 128.5 ($C$H), 146.0 ($C$), 199.9 (q, $J$ = 6.0 Hz, $C$). $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –61.0 (s, 3F). HRMS-EI ($m/z$): $[M]^+$ calcd for $C_{15}H_{15}F_3$, 252.1126; found, 252.1127.

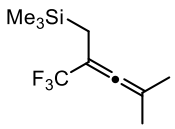
**1,1-Dimethyl-4-(3,3,3-trifluoroprop-1-en-1-ylidene)cyclohexane (1b).**




**1b**

**1b** was prepared from the corresponding ketone according to the procedure described above. $^1$H NMR (392 MHz, $CDCl_3$, δ): 0.95 (s, 3H), 0.96 (s, 3H), 1.43 (t, $J$ = 6.3 Hz, 4H), 2.17–2.30 (m, 4H), 5.22–5.30 (m, 1H). $^{13}$C NMR (99 MHz, $CDCl_3$, δ): 26.3 ($C$H$_2$), 27.9 ($C$H$_3$), 29.9 ($C$), 39.2 ($C$H$_2$), 83.2 (q, $J$ = 39.0 Hz, $C$H), 109.8 ($C$), 123.1 (q, $J$ = 271.3 Hz, $C$), 199.7 (q, $J$ = 5.7 Hz, $C$). $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –61.1 (d, $J$ = 7.1 Hz, 3F). HRMS-EI ($m/z$): $[M]^+$ calcd for $C_{11}H_{15}F_3$, 204.1126; found, 204.1126.

**Trimethyl[4-methyl-2-(trifluoromethyl)penta-2,3-dien-1-yl]silane (1c).**

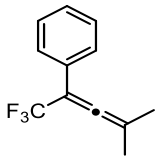



**1c**

**1c** was prepared from the corresponding ketone according to the procedure described above. $Me_3SiCH_2ZnCl$ (0.49 M in THF) was used instead of $Et_2Zn$ (1.0 M in toluene). After purification by flash silica gel column chromatography, **1c** was further purified by GPC.

$^1$H NMR (392 MHz, $CDCl_3$, δ): 0.04 (s, 9H), 1.40 (s, 2H), 1.75 (s, 6H). $^{13}$C NMR (99 MHz, $CDCl_3$, δ): –1.7 ($C$H$_3$), 14.7 ($C$H$_2$), 20.1 ($C$H$_3$), 93.2 (q, $J$ = 34.6 Hz, $C$), 102.1 ($C$), 124.2 (q, $J$ = 274.8 Hz, $C$), 200.5 (q, $J$ = 4.1 Hz, $C$). $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –65.9 (s, 3F). HRMS–FAB ($m/z$): $[M]^+$ calcd for $C_{10}H_{17}F_3Si$, 222.1052; found, 222.1056.

**(1,1,1-Trifluoro-4-methylpenta-2,3-dien-2-yl)benzene (1d).**

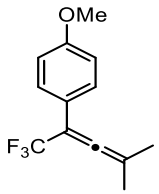



**1d**

**1d** was prepared from the corresponding ketone according to the procedure described above. PhZnCl (0.29 M in THF) was used instead of $Et_2Zn$ (1.0 M in toluene).

$^1$H NMR (396 MHz, $CDCl_3$, δ): 1.90 (s, 6H), 7.25–7.31 (m, 1H), 7.32–7.42 (m, 4H). $^{13}$C NMR (99 MHz, $CDCl_3$, δ): 19.5 (*C*H$_3$), 99.4 (q, *J* = 34.0 Hz, *C*), 105.0 (*C*), 123.7 (q, *J* = 275.4 Hz, *C*), 127.1 (*C*H), 127.7 (*C*H), 128.6 (*C*H), 131.2 (*C*), 202.3 (q, *J* = 3.8 Hz, *C*). $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –61.0 (s, 3F). HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{12}H_{11}F_3$, 212.0813; found, 212.0812.

**1-Methoxy-4-(1,1,1-trifluoro-4-methylpenta-2,3-dien-2-yl)benzene (1e).**

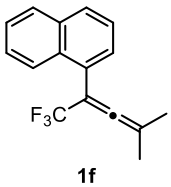



**1e**

**1e** was prepared from the corresponding ketone according to the procedure described above. {*p*-$C_6H_4$}ZnCl (0.50 M in THF) was used instead of $Et_2Zn$ (1.0 M in toluene). After purification by flash silica gel column chromatography, **1e** was further purified by GPC.

$^1$H NMR (396 MHz, $CDCl_3$, δ): 1.89 (s, 6H), 3.82 (s, 3H), 6.85–6.91 (m, 2H), 7.29–7.35 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$, δ): 19.7 (*C*H$_3$), 55.3 (*C*H$_3$), 98.8 (q, *J* = 33.5 Hz, *C*), 104.7 (*C*), 114.0 (*C*H), 123.3 (*C*), 123.4 (q, *J* = 275.3 Hz, *C*), 128.3 (*C*H), 159.2 (*C*), 201.6 (q, *J* = 4.2 Hz, *C*). $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –61.2 (s, 3F). HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{13}H_{13}F_3O$, 242.0919; found, 242.0923.

**1-(1,1,1-Trifluoro-4-methylpenta-2,3-dien-2-yl)naphthalene (1f).**

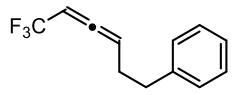



**1f**

**1f** was prepared from the corresponding ketone according to the procedure described above. (1-Naphthyl)ZnCl (0.50 M in THF) was used instead of $Et_2Zn$ (1.0 M in toluene).

$^{1}$H NMR (396 MHz, $CDCl_3$, δ): 1.87 (s, 6H), 7.46–7.57 (m, 4H), 7.85–7.89 (m, 2H), 8.09 (d, *J* = 8.3 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$, δ): 19.5 (*C*H$_3$), 95.3 (q, *J* = 35.8 Hz, *C*), 102.8 (*C*), 123.6 (q, *J* = 275.3 Hz, *C*), 125.16 (*C*H), 125.22 (*C*H), 126.0 (*C*H), 126.4 (*C*H), 127.8 (*C*H), 128.4 (*C*H), 128.9 (*C*H), 132.3 (*C*), 133.8 (*C*), 203.0 (d, *J* = 2.9 Hz, *C*). One quaternary carbon atom not observed due to signal overlapping. $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –62.7 (s, 3F). HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{16}H_{13}F_3$, 262.0969; found, 262.0972.

**(6,6,6-Trifluorohexa-3,4-dien-1-yl)benzene (1g).**

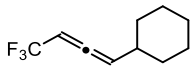


**1g**

**1g** was prepared from the corresponding aldehyde according to the procedure described above. After purification by flash silica gel column chromatography, **1g** was further purified by Kugelrohr distillation.

$^{1}$H NMR (401 MHz, $CDCl_3$, δ): 2.40–2.48 (m, 2H), 2.76 (t, *J* = 7.8 Hz, 2H), 5.37–5.45 (m, 1H), 5.67–5.76 (m, 1H), 7.16–7.24 (m, 3H), 7.27–7.33 (m, 2H). $^{13}$C NMR (99 MHz, $CDCl_3$, δ): 29.2 (*C*H$_2$), 34.7 (*C*H$_2$), 86.2 (q, *J* = 39.0 Hz, *C*H), 97.7 (*C*), 122.8 (q, *J* = 271.3 Hz, *C*), 126.2 (*C*H), 128.4 (*C*H), 146.1 (*C*), 205.2 (q, *J* = 5.7 Hz, *C*). $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –61.1 (s, 3F). HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{12}H_{11}F_3$, 212.0813; found, 212.0813.

**(4,4,4-Trifluorobuta-1,2-dien-1-yl)cyclohexane (1h).**

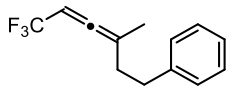


**1h**

**1h** was prepared from the corresponding aldehyde according to the procedure described above. After purification by flash silica gel column chromatography, **1h** was further purified by Kugelrohr distillation.

$^{1}$H NMR (392 MHz, $CDCl_3$, δ): 1.07–1.21 (m, 3H), 1.22–1.36 (m, 2H), 1.61–1.69 (m, 1H), 1.70–1.82 (m, 4H), 2.07–2.18 (m, 1H), 5.44 (double quint, *J* = 3.1, 6.0 Hz, 1H), 5.63–5.70 (m, 1H). $^{13}$C NMR (99 MHz, $CDCl_3$, δ): 25.8 (*C*H$_2$), 25.9 (*C*H$_2$), 32.4 (*C*H$_2$), 36.5 (*C*H), 86.5 (q, *J* = 39.0 Hz, *C*H), 104.1 (*C*H), 122.9 (q, *J* = 271.3 Hz, *C*), 204.4 (q, *J* = 7.3 Hz, *C*). $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –61.0 (t, *J* = 5.8 Hz, 3F). HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{10}H_{13}F_3$, 190.0969; found, 190.0976.

**(6,6,6-Trifluoro-3-methylhexa-3,4-dien-1-yl)benzene (1i).**

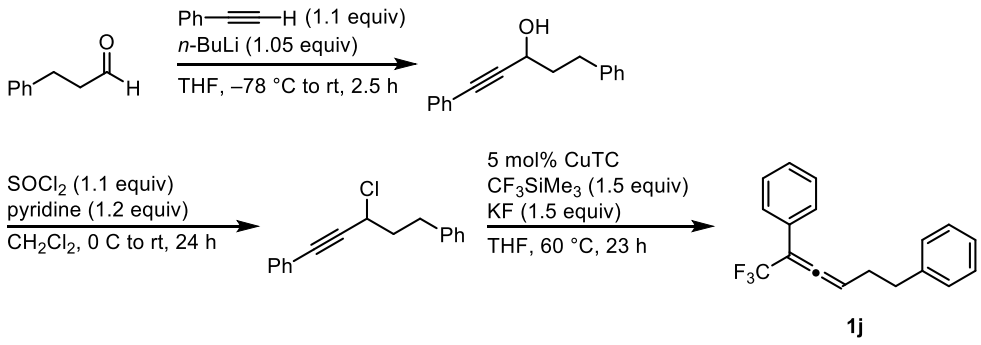


**1i**

**1i** was prepared from the corresponding ketone according to the procedure described above. After purification by flash silica gel column chromatography, **1i** was further purified by Kugelrohr distillation.

$^1$H NMR (392 MHz, $CDCl_3$, δ): 1.82 (d, $J$ = 7.8 Hz, 3H), 2.32–2.38 (m, 2H), 2.71–2.77 (m, 2H), 5.29–5.38 (m, 1H), 7.16–7.23 (m, 3H) , 7.26–7.32 (m, 2H). $^{13}$C NMR (99 MHz, $CDCl_3$, δ): 18.3 (*C*$H_3$), 33.4 (*C*$H_2$), 34.8 (*C*$H_2$), 85.4 (q, $J$ = 38.9 Hz, *C*H), 107.5 (*C*), 122.9 (q, $J$ = 271.6 Hz, *C*), 126.1 (*C*H), 128.3 (*C*H), 128.4 (*C*H), 141.1 (*C*), 202.8 (q, $J$ = 6.0 Hz, *C*). $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –61.1 (s, 3F). HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{13}H_{13}F_3$, 226.0969; found, 226.0968.

**Preparation of (6,6,6-trifluorohexa-3,4-diene-1,5-diyl)dibenzene (1j).[17-19]**




**1j**

In a vacuum dried 300 mL two necked round bottomed flask, 1.6 M solution of *n*-BuLi in hexane (13.5 mL, 21.0 mmol) was added dropwise to a solution of alkyne (2.41 mL, 22.0 mmol) in anhydrous THF (80 mL) at –78 ℃ under nitrogen atmosphere. The solution was stirred for 15 min at that temperature before the addition of 3-phenylpropionaldehyde (2.63 mL, 20.0 mmol). The mixture was allowed to warm to 0 °C gradually and stirred for an additional hour. The reaction mixture was quenched with 1 M HCl (50 mL) at 0 °C and extracted with $Et_2O$ three times. The combined organics were washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified by flash column chromatography ($SiO_2$, EtOAc/hexane, 0:100–15:85). The product was obtained in 97% yield (4.60 g, 19.5 mmol).

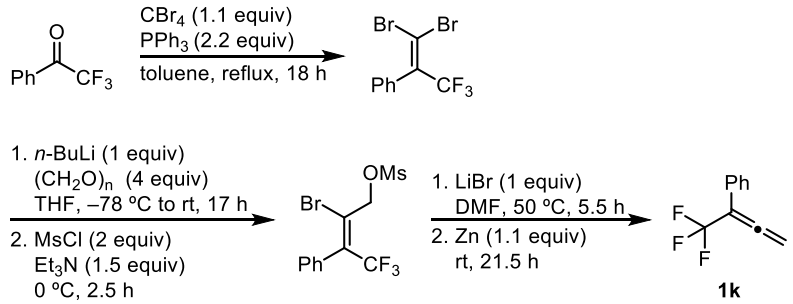
In a vacuum dried 200 mL two necked round bottomed flask, $SOCl_2$ (1.6 mL, 21.5 mmol) was added dropwise to a solution of propargyl alcohol (4.60 g, 19.5 mmol) and pyridine (1.9 mL, 23.4 mmol) in anhydrous $CH_2Cl_2$ (30 mL) at 0 ℃ under nitrogen atmosphere. The reaction mixture was stirred for 10 min at that temperature. The mixture was allowed to warm up to room temperature and stirred overnight at room temperature. The mixture was diluted with $Et_2O$ (40 mL) and washed with 1 M HCl (30 mL × 3). The water layer was extracted with $Et_2O$ three times.

The combined organics were washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered and evaporated to dryness. The crude product was purified by flash column chromatography ($SiO_2$, EtOAc/hexane, 0:100–3:97). The product was obtained in 38% yield (1.90 g, 7.46 mmol).

In a vacuum dried 200 mL two necked round bottomed flask, propargyl chloride (1.90 g, 7.46 mmol) and $CF_3SiMe_3$ (1.67 mL, 11.3 mmol) were added dropwise to a solution of Copper(I) 2-thiophenecarboxylate (71.5 mg, 0.375 mmol) and KF (658.6 mg, 11.3 mmol) in anhydrous THF (45 mL) under nitrogen atmosphere. The mixture was stirred at 60 °C for 23 h. The solution was poured into water (45 mL) and the mixture was extracted with $Et_2O$ three times. The combined extracts were washed with saturated aqueous NaCl, filtered and evaporated to dryness. After purification by flash silica gel column chromatography ($SiO_2$, hexane only), the product was further purified by GPC. **1j** was obtained in 9% yield (201.5 mg, 0.70 mmol) as a white solid.

$^1$H NMR (401 MHz, $CDCl_3$, δ): 2.48–2.65 (m, 2H), 2.77–2.90 (m, 2H), 5.97 (octet, $J$ = 3.3 Hz, 1H), 7.18–7.35 (m, 10H). $^{13}$C NMR (99 MHz, $CDCl_3$, δ): 29.8 (*C*$H_2$), 34.8 (*C*$H_2$), 99.3 (*C*H), 102.1 (q, $J$ = 34.3 Hz, *C*), 123.4 (q, $J$ = 275.4 Hz, *C*), 126.2 (*C*H), 126.8 (*C*H), 127.9 (*C*H), 128.5 (*C*H), 128.6 (*C*H), 129.9 (*C*), 140.6 (*C*), 204.3 (q, $J$ = 4.1 Hz, *C*). $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –60.9 (s, 3F). HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{18}H_{15}F_3$, 288.1126; found, 228.1128.

**Preparation of (1,1,1-trifluorobuta-2,3-dien-2-yl)benzene (1k).[20]**




In a vacuum dried 200 mL two necked round bottomed flask, $CBr_4$ (3.78 g, 11.4 mmol) was quickly added to a solution of $PPh_3$ (5.80 g, 22.1 mmol) in toluene (28 mL) under nitrogen atmosphere. After stirring for 30 min, 2,2,2-trifluoroacetophenone (1.36 mL, 10.0 mmol) was dropwise added over 15 min. The mixture was stirred for 30 min and then refluxed for 18 h. The reaction mixture was allowed to cool to room temperature, at which point hexane (20 mL) was added to precipitate salts. The suspension was filtered through Celite®, washing with hexane. Then the filtrate was quenched with water and extracted with hexane three times. The combined organics were washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified by flash silica gel column chromatography ($SiO_2$, hexane only). The product was obtained in 76% yield (2.51 g, 7.61 mmol).

In a vacuum dried 200 mL two necked round bottomed flask, 1.6 M solution of *n*-BuLi in hexane (4.76 mL, 7.61 mmol) was added dropwise to a solution of the *gem*-dibromo compound (2.51 g, 7.61 mmol) in THF (76 mL) at –78 ℃ under nitrogen atmosphere and the mixture was stirred for 40 min at that temperature. Paraformaldehyde (933.4 mg, 31.1 mmol) was added and let warm to room temperature while stirring 17 h. Then the reaction mixture was cooled to 0 ºC. $Et_3N$ (1.6 mL, 11.4 mmol) was added and stirred for 30 min, followed by dropwise addition of MsCl (1.2 mL, 15.2 mmol) and stirring for 2.5 h at this temperature. The reaction mixture was quenched with 1 M HCl (36 mL) at 0 °C and extracted with $Et_2O$ three times. The combined organics were washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified by flash silica gel column chromatography ($SiO_2$, EtOAc/hexane, 3:97–20:80). The product was obtained in 60% yield (1.65 g, 4.59 mmol).

The obtained methanesulfonyl compound (1.65 g, 4.59 mmol) and LiBr (397.2 mg, 4.57 mmol) were placed in a vacuum dried 200 mL two necked round bottomed flask. Then DMF (9.2 mL) was added under nitrogen atmosphere, and the mixture was heated to 50 ºC for 5 hours. Upon cooling to room temperature, Zn powder (334.8 mg, 5.12 mmol) was added and stirred for 22 hours. The reaction mixture was quenched with 1 M HCl (11 mL) at 0 °C and extracted with $Et_2O$ three times. The combined organics were washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified by flash column chromatography ($SiO_2$, pentane only). The product was further purified by Kugelrohr distillation. **1k** was obtained in 47% yield (396.5 mg, 2.15 mmol) as a colorless oil.

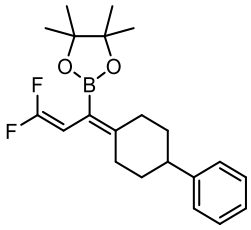
$^1$H NMR (396 MHz, $CDCl_3$, δ): 5.54 (q, $J$ = 3.4 Hz, 2H), 7.28–7.48 (m, 5H). $^{13}$C NMR (100 MHz, $CDCl_3$, δ): 83.4 (*C*$H_2$), 101.8 (q, $J$ = 34.8 Hz, *C*), 123.4 (q, $J$ = 275.0 Hz, *C*), 127.0 (*C*H), 128.2 (*C*H), 128.7 (*C*H), 129.2 (*C*H), 208.5 (q, $J$ = 3.8 Hz, *C*). $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –61.0– –60.9 (m, 3F). HRMS-EI ($m/z$): $[M]^+$ calcd for $C_{10}H_7F_3$, 184.0500; found, 184.0504.

## General Borylation Procedure and Product Characterizations

**Procedure for 2-[3,3-difluoro-1-(4-phenylcyclohexylidene)allyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3a).**

CuCl (2.5 mg, 0.025 mmol), $PPh_3$ (6.7 mg, 0.026 mmol), **1a** (126.1 mg, 0.50 mmol) and bis(pinacolato)diboron (**2**) (190.3 mg, 0.75 mmol) were placed in an oven-dried reaction vial. The vial was moved to an argon-filled glovebox. NaOMe (40.5 mg, 0.75 mmol) was placed in a

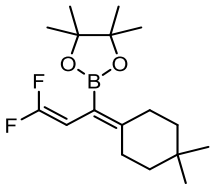
reaction vial. Then the vial was capped with a rubber septum and removed from the glovebox. Dry THF (1 mL) was added in the vial through the rubber septum using a syringe. After stirring for 3 h at 30 ºC, the reaction mixture was passed through a short silica gel column (Φ: 10 mm, height of the silica-gel column: 30 mm) eluting with $Et_2O$. The crude material was purified by flash silica gel column chromatography ($SiO_2$, $Et_2O$/hexane, 0:100–6:94) to give the corresponding borylation product **3a** as a white solid (83%, 150.0 mg, 0.415 mmol). The product contains a small amount of byproducts.



**3a**

$^1$H NMR (396 MHz, $CDCl_3$, δ): 1.31 (s, 12H), 1.45–1.68 (m, 2H), 1.93–2.05 (m, 3H), 2.12–2.23 (m, 1H), 2.70–2.81 (m, 2H), 2.93–3.00 (m, 1H), 5.15 (dd, *J* = 3.2, 27.3 Hz, 1H), 7.15–7.21 (m, 3H) , 7.24–7.31 (m, 2H). $^{13}$C NMR (99 MHz, $CDCl_3$, δ): 24.75 (*C*$H_3$), 24.81 (*C*$H_3$), 31.3 (*C*$H_2$), 34.7 (*C*$H_2$), 34.9 (*C*$H_2$), 35.6 (*C*$H_2$), 44.4 (CH), 79.9 (dd, *J* = 17.0, 25.5 Hz, *C*H), 112.5 (brs, B–C), 126.0 (*C*H), 126.7 (*C*H), 128.3 (*C*H), 146.3 (*C*), 154.1 (d, *J* = 6.5 Hz, *C*), 155.6 (dd, *J* = 288.9, 294.6 Hz, *C*). $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –89.6 (d, *J* = 34.3 Hz, 1F), –85.0 (dd, *J* = 27.4, 36.7 Hz, 1F). HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{21}H_{27}BF_2O_2$, 359.2109; found, 359.2104.

**2-[1-(4,4-Dimethylcyclohexylidene)-3,3-difluoroallyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3b).**



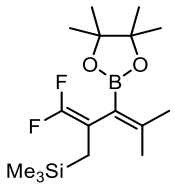
**3b**

The reaction was conducted with 100.8 mg (0.49 mmol) of **1b** for 2.5 h. The product **3b** was obtained in 89% yield (136.9 mg, 0.44 mmol).

$^1$H NMR (396 MHz, $CDCl_3$, δ): 0.95 (s, 6H), 1.30 (s, 12H), 1.35 (t, *J* = 6.3 Hz, 2H), 1.40 (t, *J* = 6.3 Hz, 2H), 2.21 (t, *J* = 6.3 Hz, 2H), 2.41 (t, *J* = 6.3 Hz, 2H), 5.11 (dd, *J* = 3.2, 27.7 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$, δ): 24.8 (*C*$H_3$), 27.4 (*C*$H_2$), 28.0 (*C*$H_3$), 30.2 (*C*), 30.8 (*C*$H_2$), 40.0 (*C*$H_2$), 40.8 (*C*$H_2$), 80.0 (dd, *J* = 17.3, 25.0 Hz, *C*H), 83.4 (*C*), 111.8 (brs, B–C), 155.6 (t, *J* = 290.8 Hz, *C*), 155.6 (t, *J* = 6.3 Hz, *C*). $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –90.1– –90.0 (m, 1F), –

85.4 (dd, $J$ = 27.4, 39.0 Hz, 1F). HRMS-EI ($m/z$): $[M]^+$ calcd for $C_{17}H_{27}BF_2O_2$, 311.2109; found, 311.2107.

**[2-(Difluoromethylene)-4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-3-en-1-yl]trimethylsilane (3c).**

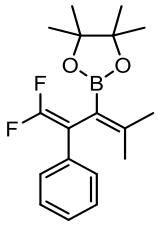



**3c**

The reaction was conducted with 55.3 mg (0.25 mmol) of **1c** for 8 h. The product **3c** was obtained in 79% yield (64.9 mg, 395 mmol).

$^1$H NMR (396 MHz, $CDCl_3$, δ): 0.00 (s, 9H), 1.26 (s, 12H), 1.40–1.44 (m, 2H), 1.76 (d, $J$ = 1.6 Hz, 3H), 2.00 (s, 3H). $^{13}$C NMR (99 MHz, $CDCl_3$, δ): –1.2 (*C*H$_3$), 18.0 (*C*H$_2$), 23.5 (d, $J$ = 1.9 Hz, *C*H$_3$), 24.0 (*C*H$_3$), 24.7 (*C*H$_3$), 82.9 (*C*), 89.3 (t, $J$ = 19.8 Hz, *C*), 150.9 (dd, $J$ = 282.8, 285.6 Hz, *C*), 151.9 (*C*). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –97.9 (d, $J$ = 54.8 Hz, 1F), –93.7 (d, $J$ = 54.8 Hz, 1F). HRMS-EI ($m/z$): $[M]^+$ calcd for $C_{16}H_{29}BF_2O_2Si$, 329.2034; found, 329.2026.

**2-(1,1-Difluoro-4-methyl-2-phenylpenta-1,3-dien-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3d).**

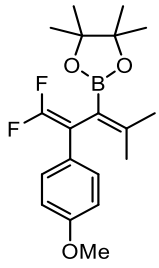



**3d**

The reaction was conducted with 105.4 mg (0.50 mmol) of **1d** for 4 h. The product **3d** was obtained in 91% yield (144.9 mg, 0.45 mmol).

$^1$H NMR (396 MHz, $CDCl_3$, δ): 1.11 (s, 12H), 1.75 (d, $J$ = 1.2 Hz, 3H), 2.11 (s, 3H), 7.19 (tt, J = 2.2, 7.0 Hz, 1H), 7.25–7.35 (m, 4H). $^{13}$C NMR (99 MHz, $CDCl_3$, δ): 23.0 (*C*H$_3$), 24.1 (*C*H$_3$), 24.4 (*C*H$_3$), 83.0 (*C*), 94.6 (dd, $J$ = 13.2, 23.6 Hz, *C*), 126.6 (*C*H), 128.0 (*C*H), 128.3 (t, $J$ = 3.8 Hz, *C*H), 134.9 (t, $J$ = 4.7 Hz, *C*), 152.3 (dd, $J$ = 286.1, 297.4 Hz, *C*), 154.6 (*C*). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –92.5 (d, $J$ = 36.6 Hz, 1F), –86.5 (d, $J$ = 38.8 Hz, 1F). HRMS-EI ($m/z$): $[M]^+$ calcd for $C_{18}H_{23}BF_2O_2$, 319.1796; found, 319.1796.

**2-[1,1-Difluoro-2-(4-methoxyphenyl)-4-methylpenta-1,3-dien-3-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3e).**

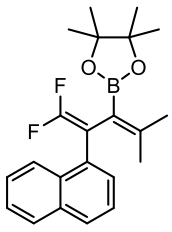



**3e**

The reaction was conducted with 120.2 mg (0.50 mmol) of **1e** for 5 h. The product **3e** was obtained in 84% yield (146.3 mg, 0.42 mmol).

$^{1}$H NMR (396 MHz, $CDCl_3$, δ): 1.12 (s, 12H), 1.74 (d, $J$ = 1.6 Hz, 3H), 2.10 (s, 3H), 3.79 (s, 3H), 6.80–6.86 (m, 2H), 7.22–7.27 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$, δ): 22.9 ($CH_3$), 24.1 ($CH_3$), 24.4 ($CH_3$), 55.1 ($CH_3$), 83.0 (*C*), 94.0 (dd, $J$ = 13.4, 23.9 Hz, *C*), 113.4 (*C*H), 127.1 (t, $J$ = 4.8 Hz, *C*), 129.3 (t, $J$ = 3.8 Hz, *C*H), 152.1 (dd, $J$ = 285.5, 296.1 Hz, *C*), 154.1 (*C*), 158.2 (*C*). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –93.7 (d, $J$ = 41.0 Hz, 1F), –87.9 (d, $J$ = 38.8 Hz, 1F). HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{19}H_{25}BF_2O_3$, 349.1901; found, 349.1911.

**2-[1,1-Difluoro-4-methyl-2-(naphthalen-1-yl)penta-1,3-dien-3-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3f).**



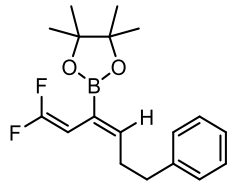

**3f**

The reaction was conducted with 131.1 mg (0.50 mmol) of **1f** for 25 h. The product **3f** was obtained in 85% yield (158.1 mg, 0.43 mmol).

$^{1}$H NMR (401 MHz, $CDCl_3$, δ): 0.92 (s, 12H), 1.90 (d, $J$ = 2.4 Hz, 3H), 2.08 (s, 3H), 7.31–7.53 (m, 4H), 7.72–7.84 (m, 2H), 8.09 (dd, $J$ = 3.8, 8.2 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$, δ): 23.2 (d, $J$ = 2.0 Hz, $CH_3$), 24.2 ($CH_3$), 24.4 ($CH_3$), 83.0 (*C*), 94.4 (dd, $J$ = 17.7, 23.5 Hz, *C*), 125.0 (*C*H), 125.5 (*C*H), 125.6 (*C*H), 126.4 (d, $J$ = 1.9 Hz, *C*H), 127.9 (*C*H), 128.0 (d, $J$ = 2.8 Hz, *C*H), 128.1 (*C*H), 131.3 (*C*), 132.5 (t, $J$ = 3.3 Hz, *C*), 133.6 (*C*), 151.5 (dd, $J$ = 289.8, 293.7 Hz, *C*), 152.0 (*C*). The carbon directly attached to the boron atom was not detected, likely due to

quadrupolar relaxation. $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –88.3 (d, $J$ = 36.6 Hz, 1F), –87.7 (d, $J$ = 34.3 Hz, 1F). HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{22}H_{25}BF_2O_2$, 369.1952; found, 369.1959.

**(*Z*)-2-(1,1-Difluoro-6-phenylhexa-1,3-dien-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane [(*Z*)-3g].**

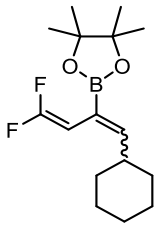


(*Z*)-**3g**

The reaction was conducted with 106.3 mg (0.50 mmol) of **1g** for 5 h. The product (*Z*)-**3g** was obtained in 50% yield (80.1 mg, 0.25 mmol, *Z*/*E* = 94/6) with small amount of byproducts. *Z*/*E* ratio was determined by $^{19}$F NMR analysis of crude mixture.

$^1$H NMR (396 MHz, $CDCl_3$, δ): 1.28 (s, 12H), 2.44 (q, $J$ = 7.8 Hz, 2H), 2.69–2.76 (m, 2H), 4.98 (dd, $J$ = 1.2, 26.5 Hz, 1H), 6.36 (t, $J$ = 6.9 Hz, 1H), 7.16–7.22 (m, 3H), 7.26–7.32 (m, 2H). $^{13}$C NMR (99 MHz, $CDCl_3$, δ): 24.6 (*C*$H_3$), 31.8 (*C*$H_2$), 34.8 (*C*$H_2$), 78.1 (dd, $J$ = 18.4, 26.9 Hz, *C*H), 83.7 (*C*), 126.0 (*C*H), 128.3 (*C*H), 128.4 (*C*H), 141.5 (*C*), 146.7 (d, $J$ = 4.7 Hz, *C*H), 155.1 (dd, $J$ = 289.4, 296.0 Hz, *C*). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –87.1 (d, $J$ = 29.5 Hz, 1F), –82.4 (t, $J$ = 30.5 Hz, 1F). HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{18}H_{23}BF_2O_2$, 319.1796; found, 319.1790.

**2-(1-Cyclohexyl-4,4-difluorobuta-1,3-dien-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3h).**



**3h**

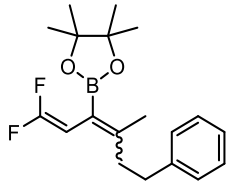
The reaction was conducted with 95.1 mg (0.50 mmol) of **1h** for 5.5 h. The product **3h** was purified by GPC and obtained in 49% yield (73.8 mg, 0.25 mmol, *Z*/*E* = 69/31). *Z*/*E* ratio was determined by $^{19}$F NMR analysis of crude mixture.

For major isomer: $^1$H NMR (396 MHz, $CDCl_3$, δ): 1.01–1.24 (m, 5H), 1.28 (s, 12H), 1.58–1.76 (m, 5H), 2.21–2.32 (m, 1H), 5.05 (dq, $J$ = 1.5, 26.8 Hz, 1H), 6.08 (d, $J$ = 9.5 Hz, 1H). $^{13}$C NMR (99 MHz, $CDCl_3$, δ): 24.5 (*C*$H_3$), 25.7 (*C*$H_2$), 25.7 (*C*$H_2$), 32.0 (*C*$H_2$), 38.6 (*C*H), 78.1 (dd, $J$ =

17.9, 26.4 Hz, *C*H), 83.5 (*C*), 152.9 (d, *J* = 4.9 Hz, *C*H), 155.6 (t, *J* = 292.7 Hz, *C*). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –87.7 (d, *J* = 32.1 Hz, 1F), –82.9 (dd, *J* = 27.6, 32.1 Hz, 1F). HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{16}H_{25}BF_2O_2$, 297.1952; found, 297.1952.

For minor isomer: $^1$H NMR (396 MHz, $CDCl_3$, δ): 1.01–1.24 (m, 5H), 1.31 (s, 12H), 1.58–1.76 (m, 5H), 2.33–2.42 (m, 1H), 4.91 (dd, *J* = 3.0, 27.1 Hz, 1H), 5.88 (d, *J* = 9.5 Hz, 1H). $^{13}$C NMR (99 MHz, $CDCl_3$, δ): 24.7 (*C*$H_3$), 25.8 (*C*$H_2$), 25.9 (*C*$H_2$), 33.2 (*C*$H_2$), 40.6 (*C*H), 83.7 (*C*), 84.5 (dd, *J* = 16.0, 26.4 Hz, *C*H), 151.0 (dd, *J* = 3.9, 8.9 Hz, *C*), 155.2 (t, *J* = 292.2 Hz, *C*). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –91.0– –90.9 (m, 1F), –85.1 (dd, *J* = 26.1, 37.7 Hz, 1F).

**2-(1,1-Difluoro-4-methyl-6-phenylhexa-1,3-dien-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3i).**



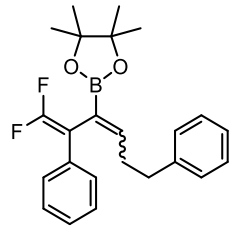

**3i**

The reaction was conducted with 113.0 mg (0.50 mmol) of **1i** for 6 h. The product **3i** was obtained in 87% yield (145.7 mg, 0.44 mmol, *E*/*Z* = 42/58). *E*/*Z* ratio was determined by $^{19}$F NMR analysis of crude mixture.

For major isomer: $^1$H NMR (396 MHz, $CDCl_3$, δ): 1.29 (s, 12H), 1.82 (s, 3H), 2.55–2.62 (m, 2H), 2.65–2.77 (m, 2H), 5.06 (dt, *J* = 3.5, 27.2 Hz, 1H), 7.16–7.31 (m, 5H). $^{13}$C NMR (99 MHz, $CDCl_3$, δ): 19.9 (*C*$H_3$), 24.85 (*C*$H_3$), 35.7 (*C*$H_2$), 40.9 (*C*$H_2$), 80.7 (dd, *J* = 17.0, 25.5 Hz, *C*H), 83.5 (*C*), 125.8 (*C*H), 128.2–128.4 (m, *C*H), 142.1 (*C*), 151.9 (d, *J* = 5.7 Hz, *C*), 155.2 (dd, *J* = 288.9, 294.6 Hz, *C*). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –89.5 (d, *J* = 36.6 Hz, 1F), –84.5– –84.3 (m, 1F). HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{19}H_{25}BF_2O_2$, 333.1952; found, 333.1950.

For minor isomer: $^1$H NMR (396 MHz, $CDCl_3$, δ): 1.32 (s, 12H), 2.01 (s, 3H), 2.36–2.43 (m, 2H), 2.65–2.77 (m, 2H), 5.06 (dt, *J* = 3.5, 27.2 Hz, 1H), 7.16–7.31 (m, 5H). $^{13}$C NMR (99 MHz, $CDCl_3$, δ): 22.5 (*C*$H_3$), 24.80 (*C*$H_3$), 33.9 (*C*$H_2$), 37.7 (*C*$H_2$), 80.1 (dd, *J* = 17.4, 25.9 Hz, *C*H), 83.6 (*C*), 125.9 (*C*H), 128.2–128.4 (m, *C*H), 141.7 (*C*), 150.9 (d, *J* = 6.6 Hz, *C*), 155.5 (dd, *J* = 288.9, 293.7 Hz, *C*). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –89.7 (d, *J* = 36.6 Hz, 1F), –84.5– –84.3 (m, 1F).

**2-(1,1-Difluoro-2,6-diphenylhexa-1,3-dien-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3j).**



**3j**

The reaction was conducted with 144.8 mg (0.50 mmol) of **1j** for 6.5 h. The product **3j** was purified by GPC and obtained in 45% yield (90.4 mg, 0.23 mmol, *Z*/*E* = 79/21) with small amount of byproducts. *Z*/*E* ratio was determined by $^{19}$F NMR analysis of crude mixture.

For major isomer: $^{1}$H NMR (396 MHz, $CDCl_3$, δ): 1.17 (s, 12H), 2.38 (q, *J* = 7.8 Hz, 2H), 2.62–2.71 (m, 2H), 6.72 (t, *J* = 7.3 Hz, 1H), 7.05–7.33 (m, 10H). $^{13}$C NMR (99 MHz, $CDCl_3$, δ): 24.4 (*C*$H_3$), 32.6 (*C*$H_2$), 34.6 (*C*$H_2$), 83.5 (*C*), 92.2 (dd, *J* = 14.2, 23.7 Hz, *C*), 125.9 (*C*H), 126.7 (*C*H), 127.9–128.4(m, *C*H), 128.5 (*C*H), 129.5 (t, *J* = 2.8 Hz, *C*H), 134.3 (t, *J* = 4.7 Hz, *C*), 141.5 (*C*), 150.5 (*C*H), 152.0 (dd, *J* = 287.5, 297.9 Hz, *C*). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –91.2 (d, *J* = 34.3 Hz, 1F), –85.2 (d, *J* = 34.3 Hz, 1F). HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{24}H_{27}BF_2O_2$, 395.2109; found, 395.2122.

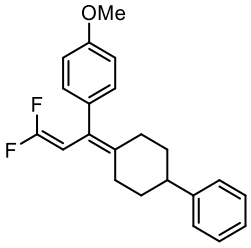
For minor isomer: $^{1}$H NMR (396 MHz, $CDCl_3$, δ): 1.18 (s, 12H), 2.38 (q, *J* = 7.8 Hz, 2H), 2.62–2.71 (m, 2H), 6.02–6.16 (m, 1H), 7.05–7.33 (m, 10H). $^{13}$C NMR (99 MHz, $CDCl_3$, δ): 24.6 (*C*$H_3$), 33.6 (*C*$H_2$), 36.0 (*C*$H_2$), 83.5 (*C*), 92.2 (dd, *J* = 14.2, 23.7 Hz, *C*), 125.8 (*C*H), 127.1 (*C*H), 127.9–128.4 (m, *C*H), 128.6 (*C*H), 129.7 (*C*H), 134.3 (t, *J* = 4.7 Hz, *C*), 141.6 (*C*), 150.5 (*C*H), 152.0 (dd, *J* = 287.5, 297.9 Hz, *C*). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –91.3 (d, *J* = 36.9 Hz, 1F), –88.2 (d, *J* = 36.6 Hz, 1F).

## 4. Cross-Coupling Reaction Procedure and Product Characterizations

**Procedure for 1-[3,3-difluoro-1-(4-phenylcyclohexylidene)allyl]-4-methoxybenzene (4a).[7]**

$Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 5.0 mol%), SPhos (4.0 mg, 0.010 mmol, 10 mol%), **3a** (36.2 mg, 0.10 mmol) were placed in an oven-dried reaction vial. The flask was then evacuated and backfilled with nitrogen three times. THF (0.21 mL), aqueous NaOH (0.12 mL of 2.5 M solution in $H_2O$, 0.30 mmol) and 4-bromoanisole (28.5 mg, 0.15 mmol) were added to the flask. The resulting solution was stirred at 60 ºC for 25 h. After the reaction, the mixture was extracted with

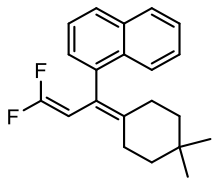
$Et_2O$ and the organic layer was dried over $MgSO_4$. After filtration, all of the volatiles were removed by rotary evaporator. The crude material was purified by flash silica gel column chromatography ($SiO_2$, $Et_2O$/hexane, 0:100–2:98). **4a** was obtained in 75% yield (25.8 mg, 0.076 mmol) as a colorless oil.




**4a**

$^1$H NMR (396 MHz, $CDCl_3$, δ): 1.40–1.70 (m, 2H), 1.85–2.19 (m, 4H), 2.54–2.62 (m, 1H), 2.68–2.87 (m, 2H), 3.81 (s, 3H), 5.17 (dd, *J* = 4.4, 25.3 Hz, 1H), 6.84–6.89 (m, 2H), 7.07–7.11 (m, 2H), 7.16–7.33 (m, 5H). $^{13}$C NMR (99 MHz, $CDCl_3$, δ): 31.6 (*C*$H_2$), 35.1 (*C*$H_2$), 35.5 (*C*$H_2$), 44.5 (*C*H), 55.2 (*C*$H_3$), 81.2 (dd, *J* = 14.2, 26.4 Hz, *C*H), 113.4 (*C*H), 122.1 (t, *J* = 4.7 Hz, *C*), 126.1 (*C*H), 126.8 (*C*H), 128.4 (*C*H), 130.2 (*C*H), 132.8 (*C*), 139.9 (dd, *J* = 1.9, 5.6 Hz, *C*), 146.6 (*C*), 155.6 (dd, *J* = 288.0, 298.4 Hz, *C*), 158.2 (*C*). $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –87.5 (d, *J* = 29.8 Hz, 1F), –83.3 (dd, *J* = 26.5, 31.0 Hz, 1F). HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{22}H_{22}F_2O$, 340.1639; found, 340.1635.

**1-[1-(4,4-Dimethylcyclohexylidene)-3,3-difluoroallyl]naphthalene (4b).**

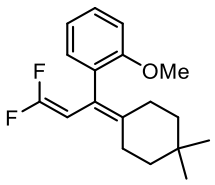



**4b**

The reaction was conducted with 31.4 mg (0.10 mmol) of **3b** and the corresponding aryl bromide for 18 h. The product **4b** was obtained in 61% yield (19.1 mg, 0.061 mmol).

$^1$H NMR (396 MHz, $CDCl_3$, δ): 0.95 (s, 6H), 1.15 (t, *J* = 6.3 Hz, 2H), 1.51 (q, *J* = 5.5 Hz, 2H), 1.74–1.88 (m, 2H), 2.46 (t, *J* = 6.3 Hz, 2H), 5.32 (dd, *J* = 4.6, 24.8 Hz, 1H), 7.23 (d, *J* = 6.7 Hz, 1H), 7.41–7.49 (m, 3H), 7.75–7.87 (m, 3H). $^{13}$C NMR (99 MHz, $CDCl_3$, δ): 26.9 (*C*$H_3$), 27.90 (*C*$H_3$), 27.95 (*C*$H_2$), 28.2 (*C*$H_2$), 30.3 (*C*), 40.4 (*C*$H_2$), 40.5 (*C*$H_2$), 81.0 (dd, *J* = 12.8, 27.8 Hz, *C*H), 119.8 (t, *J* = 5.2 Hz, *C*), 125.43 (*C*H), 125.46 (*C*H), 125.6 (*C*H), 125.8 (*C*H), 126.4 (*C*H), 127.1 (*C*H), 128.3 (*C*H), 131.9 (*C*), 133.5 (*C*), 138.5 (*C*), 142.6 (q, *J* = 3.1 Hz, *C*), 155.5 (t, *J* = 293.6 Hz, *C*). $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –87.5 (dd, *J* = 4.7, 31.9 Hz, 1F), –83.5 (dd, *J* = 25.2, 29.7 Hz, 1F). HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{21}H_{22}F_2$, 312.1690; found, 312.1695.

**1-[1-(4,4-Dimethylcyclohexylidene)-3,3-difluoroallyl]-2-methoxybenzene (4c).**

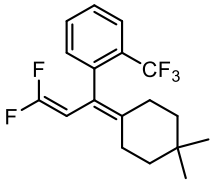



**4c**

The reaction was conducted with 31.3 mg (0.100 mmol) of **3b** and the corresponding aryl bromide for 27 h. The product **4c** was obtained in 50% yield (14.8 mg, 0.0506 mmol).

$^{1}$H NMR (392 MHz, $CDCl_3$, δ): 0.94 (s, 3H), 0.95 (s, 3H), 1.17–1.32 (m, 2H), 1.35–1.51 (m, 2H), 1.88–2.02 (m, 2H), 2.30–2.37 (m, 2H), 3.79 (s, 3H), 5.23 (dd, *J* = 4.5, 25.3 Hz, 1H), 6.86–6.94 (m, 2H), 7.00–7.06 (m, 1H), 7.22–7.28 (m, 1H). $^{13}$C NMR (99 MHz, $CDCl_3$, δ): 26.9 (*C*$H_2$), 27.6 (*C*$H_3$), 27.7 (*C*$H_2$), 28.7 (*C*$H_3$), 30.3 (*C*), 40.2 (*C*$H_2$), 40.4 (*C*$H_2$), 55.5(*C*$H_3$), 80.4 (dd, *J* = 13.3, 27.4 Hz, *C*H), 110.7 (*C*H), 118.1 (t, *J* = 4.8 Hz, *C*H), 120.3 (*C*H), 128.1 (*C*H), 129.3 (*C*), 130.9 (*C*H), 141.7 (dd, *J* = 2.8, 6.6 Hz, *C*), 155.4 (dd, *J* = 287.0, 298.4 Hz, *C*), 157.0 (*C*). $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –88.4 (dd, *J* = 4.8, 32.1 Hz, 1F), –85.1 (dd, *J* = 25.0, 32.1 Hz, 1F). HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{18}H_{22}F_2O$, 292.1639; found, 262.1638.

**1-(1-(4,4-Dimethylcyclohexylidene)-3,3-difluoroallyl)-2-(trifluoromethyl)benzene (4d).**

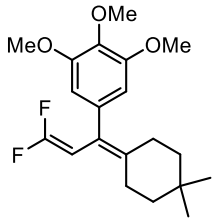



**4d**

The reaction was conducted with 31.9 mg (0.102 mmol) of **3b** and the corresponding aryl bromide for 21 h. The product **4d** was obtained in 62% yield (21.0 mg, 0.064 mmol).

$^{1}$H NMR (396 MHz, $CDCl_3$, δ): 0.93 (s, 3H), 0.95 (s, 3H), 1.08–1.18 (m, 1H), 1.19–1.29 (m, 1H), 1.32–1.49 (m, 2H), 1.70–1.85 (m, 2H), 2.25–2.40 (m, 2H), 5.26 (dd, *J* = 4.8, 24.6 Hz, 1H), 7.16 (d, *J* = 7.9 Hz, 1H), 7.34–7.41 (m, 1H), 7.46–7.53 (m, 1H), 7.66 (d, *J* = 7.9 Hz, 1H). $^{13}$C NMR (99 MHz, $CDCl_3$, δ): 26.6 (*C*$H_2$), 27.7 (*C*$H_3$), 28.1 (*C*$H_2$), 28.4 (*C*$H_3$), 30.1 (*C*), 39.7 (*C*$H_2$), 40.0 (*C*$H_2$), 80.8 (dd, *J* = 12.3, 29.3 Hz, *C*H), 119.3 (t, *J* = 5.2 Hz, *C*), 124.2 (q, *J* = 275.1 Hz, *C*), 126.0 (q, *J* = 5.0 Hz, *C*H), 127.0 (*C*H), 128.7 (q, *J* = 28.6 Hz, *C*), 131.5 (*C*H), 131.6 (*C*H), 139.5 (*C*), 142.0–142.2 (m, *C*), 155.6 (dd, *J* = 287.1, 299.3 Hz, *C*). $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –87.6 (d, *J* = 38.0 Hz, 1F), –84.3 (t, *J* = 29.1 Hz, 1F), –60.9 (s, 3F). HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{18}H_{19}F_5$, 330.1407; found, 330.1396.

**5-[1-(4,4-Dimethylcyclohexylidene)-3,3-difluoroallyl]-1,2,3-trimethoxybenzene (4e).**

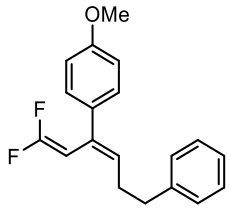



**4e**

The reaction was conducted with 31.2 mg (0.10 mmol) of **3b** and the corresponding aryl bromide for 20 h. The product **4e** was obtained in 83% yield (29.1 mg, 0.083 mmol).

$^{1}$H NMR (396 MHz, $CDCl_3$, δ): 0.96 (s, 6H), 1.28 (t, *J* = 6.3 Hz, 2H), 1.43 (t, *J* = 6.3 Hz, 2H), 2.11 (t, *J* = 6.3 Hz, 2H), 2.30 (t, *J* = 5.9 Hz, 2H), 3.84 (s, 6H), 3.86 (s, 3H), 5.11 (dd, *J* = 4.0, 25.3 Hz, 1H), 6.33 (s, 2H). $^{13}$C NMR (99 MHz, $CDCl_3$, δ): 27.5 ($CH_2$), 27.7 ($CH_2$), 28.1 ($CH_3$), 30.3 (*C*), 40.1 ($CH_2$), 40.7 ($CH_2$), 56.0 ($CH_3$), 60.9 ($CH_3$), 80.9 (dd, *J* = 14.7, 26.9 Hz, *C*H), 106.1 (*C*H), 108.8 (*C*), 121.9 (t, *J* = 4.7 Hz, *C*), 136.4 (*C*), 136.5 (*C*), 141.5 (dd, *J* = 1.9, 5.6 Hz, *C*), 152.8 (*C*), 155.4 (dd, *J* = 287.9, 298.3 Hz, *C*). $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –87.6 – –87.5 (m, 1F), –83.1 (dd, *J* = 25.0, 29.8 Hz, 1F). HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{20}H_{26}F_2O_3$, 352.1850; found, 352.1846.

**(*E*)-1-(1,1-Difluoro-6-phenylhexa-1,3-dien-3-yl)-4-methoxybenzene [(*E*)- 4f].**



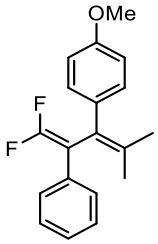

(*E*)-**4f**

The reaction was conducted with 32.0 mg (0.10 mmol) of **3g** and the corresponding aryl bromide for 20 h. The product (*E*)-**4f** was obtained in 59 % yield (17.6 mg, 0.059 mmol, *E*/*Z* = 94/6) with small amount of byproducts. *E/Z* ratio was determined by $^{19}$F NMR analysis of crude mixture.

$^{1}$H NMR (396 MHz, $CDCl_3$, δ): 2.50 (q, *J* = 7.8 Hz, 2H), 2.78 (t, *J* = 7.7 Hz, 2H), 3.81 (s, 3H), 4.99 (dd, *J* = 2.4, 26.1 Hz, 1H), 5.79 (t, *J* = 7.1 Hz, 1H), 6.81–6.87 (m, 2H), 7.16–7.33 (m, 7H). $^{13}$C NMR (99 MHz, $CDCl_3$, δ): 31.4 ($CH_2$), 35.5 ($CH_2$), 55.2 ($CH_3$), 78.3 (dd, *J* = 16.1, 27.4 Hz, *C*H), 113.5 (*C*H), 125.9 (*C*H), 127.7 (*C*H), 128.36 (*C*H), 128.45 (*C*H), 129.2–129.4 (m, *C*), 130.6 (d, *J* = 2.8 Hz, *C*), 133.3 (*C*), 141.6 (*C*), 155.8 (dd, *J* = 290.4, 297.9 Hz, *C*), 158.9 (*C*). $^{19}$F NMR

(373 MHz, $CDCl_3$, δ): –85.6 (d, $J$ = 29.5 Hz, 1F), –80.4 (t, $J$ = 26.3 Hz, 1F). HRMS-EI ($m/z$): $[M]^+$ calcd for $C_{19}H_{18}F_2O$, 300.1326; found, 300.1325.

**1-(1,1-Difluoro-4-methyl-2-phenylpenta-1,3-dien-3-yl)-4-methoxybenzene (4g).**

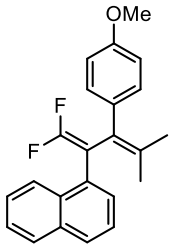



**4g**

The reaction was conducted with 32.4 mg (0.10 mmol) of **3d** and the corresponding aryl bromide for 20 h. The product **4g** was obtained in 54% yield (16.3 mg, 0.054 mmol).

$^1$H NMR (396 MHz, $CDCl_3$, δ): 1.83 (s, 3H), 1.87 (s, 3H), 3.75 (s, 3H), 6.74–6.78 (m, 2H), 7.04–7.09 (m, 2H), 7.15–7.21 (m, 1H), 7.25–7.34 (m, 4H). $^{13}$C NMR (99 MHz, $CDCl_3$, δ): 21.7 (*C*$H_3$), 22.1 (*C*$H_3$), 55.1 (*C*$H_3$), 95.7 (dd, $J$ = 13.2, 23.6 Hz, *C*), 113.2 (*C*H), 126.9 (*C*H), 128.2 (t, $J$ = 4.3 Hz, *C*H), 128.3 (*C*H), 130.3 (*C*H), 132.7 (*C*), 133.0 (t, $J$ = 4.3 Hz, *C*), 135.5 (*C*), 153.2 (dd, $J$ = 287.0, 299.3 Hz, *C*), 156.2 (*C*), 158.0 (*C*). $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –91.6 (d, $J$ = 34.3 Hz, 1F), –86.2 (d, $J$ = 32.1 Hz, 1F). HRMS-EI ($m/z$): $[M]^+$ calcd for $C_{19}H_{18}F_2O$, 300.1326; found, 300.1324.

**1-[1,1-Difluoro-3-(4-methoxyphenyl)-4-methylpenta-1,3-dien-2-yl]naphthalene (4h).**



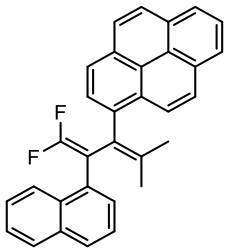

**4h**

The reaction was conducted with 36.9 mg (0.0997 mmol) of **3f** and the corresponding aryl bromide for 6.5 h. The product **4h** was obtained in 76% yield (26.4 mg, 0.075 mmol).

$^1$H NMR (396 MHz, $CDCl_3$, δ): 1.74 (s, 3H), 2.13 (d, $J$ = 2.0 Hz, 3H), 3.66 (s, 3H), 6.57–6.64 (m, 2H), 6.83–6.89 (m, 2H), 7.21–7.26 (m, 1H), 7.33 (t, $J$ = 7.7 Hz, 1H), 7.38–7.44 (m, 2H), 7.70 (d, $J$ = 8.3 Hz, 1H), 7.74–7.79 (m, 1H), 7.81–7.87 (m, 1H). $^{13}$C NMR (99 MHz, $CDCl_3$, δ): 21.9 (*C*$H_3$), 22.3 (d, $J$ = 2.8 Hz, *C*$H_3$), 55.0 (*C*$H_3$), 93.2 (dd, $J$ = 17.9, 22.7 Hz, *C*), 113.0 (*C*H), 125.0 (*C*H), 125.1 (d, $J$ = 1.9 Hz, *C*H), 125.5 (*C*H), 125.9 (*C*H), 127.9 (d, $J$ = 1.9 Hz, *C*H), 128.1 (*C*H), 128.3 (*C*H), 128.8 (t, $J$ = 2.9 Hz, *C*), 130.4 (*C*H), 130.9 (t, $J$ = 3.3 Hz, *C*), 131.6 (*C*), 132.4 (d, $J$

= 1.9 Hz, *C*), 133.6 (*C*), 134.2 (*C*), 152.1 (dd, *J* = 290.8, 294.6 Hz, *C*), 157.9 (*C*). $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –88.5 (d, *J* = 29.8 Hz, 1F), –87.9 (d, *J* = 29.5 Hz, 1F). HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{23}H_{20}F_2O$, 350.1482; found, 350.1483.

**1-[1-(4,4-Dimethylcyclohexylidene)-3,3-difluoro-2-(naphthalen-1-yl)allyl]pyrene (4i).**




**4i**

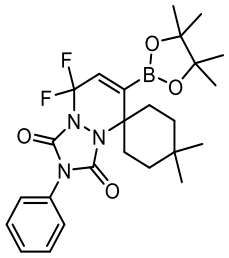
The reaction was conducted with 37.6 mg (0.102 mmol) of **3f** and the corresponding aryl bromide for 23 h. The product **4i** was obtained in 55% yield (24.9 mg, 0.056 mmol).

$^1$H NMR (392 MHz, $CDCl_3$, δ): 1.54 (s, 3H), 2.40 (d, *J* = 2.4 Hz, 3H), 7.01–7.09 (m, 1H), 7.14 (t, *J* = 7.4 Hz, 1H), 7.22–7.35 (m, 4H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.68 (d, *J* = 8.2 Hz, 1H), 7.78 (d, *J* = 7.8 Hz, 1H), 7.88 (d, *J* = 8.6 Hz, 1H), 7.93–7.98 (m, 3H), 8.03 (d, *J* = 9.4 Hz, 1H), 8.11 (d, *J* = 7.8 Hz, 2H). $^{13}$C NMR (99 MHz, $CDCl_3$, δ): 22.1 ($CH_3$), 22.2 (d, *J* = 2.8 Hz, $CH_3$), 93.7 (t, *J* = 20.3 Hz, *C*), 124.2 (*C*H), 124.6 (*C*), 124.7 (*C*H), 124.8 (*C*H), 124.88 (*C*H), 124.95 (*C*H), 125.5 (*C*H), 125.7 (*C*H), 125.9 (*C*H), 126.9 (*C*H), 127.1 (*C*), 127.2 (*C*H), 127.3 (*C*H), 127.4 (*C*H), 128.0 (*C*H), 128.17 (*C*H), 128.20 (*C*H), 129.1 (*C*), 130.0 (*C*), 130.4 (*C*), 130.9 (*C*), 131.1 (*C*), 131.9 (*C*), 133.4 (*C*), 135.4 (*C*), 136.5 (*C*), 151.9 (t, *J* = 292.7 Hz, *C*). $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –89.4 (d, *J* = 31.7 Hz, 1F), –86.7– –86.4 (m, 1F). HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{32}H_{22}F_2$, 444.1690; found, 444.1689.

## 5. Diels–Alder Reaction Procedure and Product Characterization

Diels Alder reaction was performed according to the reported procedure.[9c] 4-Phenyl-1,2,4-triazoline-3,5-dione (69.3 mg, 0.40 mmol) was placed in an oven-dried reaction vial. The flask was then evacuated and backfilled with nitrogen three times. Toluene (0.48 mL) and **3b** (31.0 mg, 0.10 mmol) were added to the reaction vial, and the resulting solution was stirred at room temperature for 21 h. After the reaction mixture was passed through a short silica gel column eluting with $Et_2O$. The crude material was purified by flash silica gel column chromatography

($SiO_2$, EtOAc/hexane, 0:100– 15:85). **6** was obtained in 30% yield (14.7 mg, 0.030 mmol) as a white solid.



**6**

$^1$H NMR (392 MHz, $CDCl_3$, δ): 0.97 (s, 3H), 1.04 (s, 3H), 1.34 (s, 12H), 1.35–1.44 (m, 2H), 1.67–1.78 (m, 2H), 2.06–2.17 (m, 2H), 2.34 (dt, *J* = 4.4, 14.8 Hz, 2H), 6.28 (t, *J* = 3.7 Hz, 1H), 7.38–7.43 (m, 1H), 7.45–7.53 (m, 4H). $^{13}$C NMR (99 MHz, $CDCl_3$, δ): 24.7 (*C*$H_3$), 25.8 (*C*$H_3$), 28.3 (*C*$H_2$), 29.0 (*C*), 30.7 (*C*$H_3$), 34.4 (*C*$H_2$), 64.8 (*C*), 85.0 (*C*), 113.5 (t, *J* = 251.6 Hz, *C*), 120.9 (*C*), 126.1 (*C*H), 126.7 (t, *J* = 29.7 Hz, *C*), 128.7 (*C*H), 129.2 (*C*H), 130.5 (*C*), 150.6 (d, *J* = 25.4 Hz, *C*). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. $^{19}$F NMR (373 MHz, $CDCl_3$, δ): –83.25– –83.20 (m, 2F). HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{25}H_{32}BF_2N_3O_4$, 486.2490; found 486.2496.

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# Chapter 3.

# Dearomatization/Enantioselective Borylation Sequence for the Synthesis of Fluorine-Containing *N*-heterocyclic Boronates

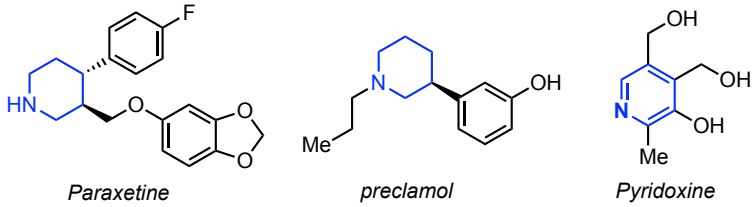
## Abstract

The author has developed a novel method for the synthesis of chiral fluorine-containing *N*-heterocyclic boronates via dearomatization through partial reduction of 4-$CF_3$-pyridine followed by copper(I)-catalyzed enantioselective borylation sequence. Notably, chiral $CF_2$-containing organoboronates were obtained with stoichiometric amount of base via copper(I)-β-fluoroelimination, whereas $CF_3$-containing boronates were obtained via protoborylation with proton source separately. The products in this reaction were able to transform into several chiral fluorine-containing *N*-heterocyclic compounds, which would be inaccessible by any other methods


## Introduction

The incorporation of fluorine atom(s) into small molecules can lead to dramatic change in the molecule's physical and chemical properties.[1] In this context, incorporation of fluorine atom(s) into *N*-heterocyclic compounds would be highly attractive[2] with the point of view from medicinal chemistry, because these compounds are important structural motifs that can be found in an array of naturally occurring bioactive molecules and pharmaceutical drugs (Figure 1).[3] As such, development of efficient method for the synthesis of these fluorine-containing *N*-heterocyclic compounds are important and remain highly desired.[4]

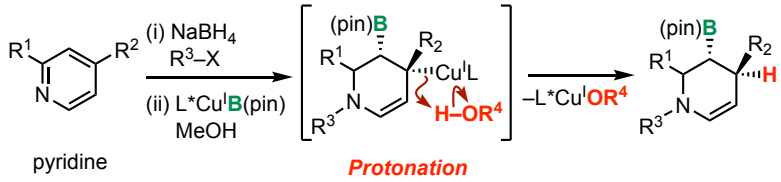
***Figure 1.*** Representative examples of bioactive *N*-heterocyclic compounds




Optically active organoboron compounds are attractive synthons that have great potential for the flexible assembly of an array of structurally diverse compounds, due to the stereospecific transformability of C–B bond.[5] Along lines, my group recently has been interested in applying a copper(I)-catalyzed enantioselective borylation reaction for the synthesis of chiral *N*-heterocyclic organoborotaes that are attracted considerable interest which would afford the several bioactive chiral *N*-heterocyclic organocompounds.[6] In 2016, my group have reported partial reduction/enantioselective borylation sequence of pyridine by using a capper(I) catalyst to furnish the corresponding chiral 3-boryl-tetrahydropyridines (Scheme 1a).[6c] This rection proceeded via enantioselective insertion of boryl-copper(I) intermediate for 1,2-dihydropyiridines, followed by protonation of the allyl copper(I) intermediate. The dearomatization of pyridines

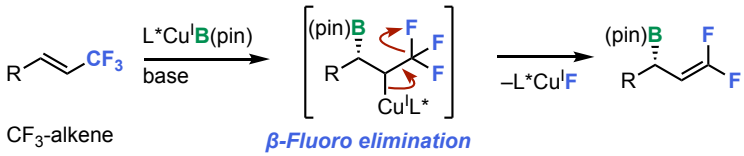
derivatives represents can provide direct access to various chiral *N*-heterocyclic structures from readily available compounds,[7] which represents a powerful method for the *N*-heterocyclic bioactive compounds

***Scheme 1.*** The partial reduction/copper(I)-catalyzed enantioselective borylation sequence of pyridine



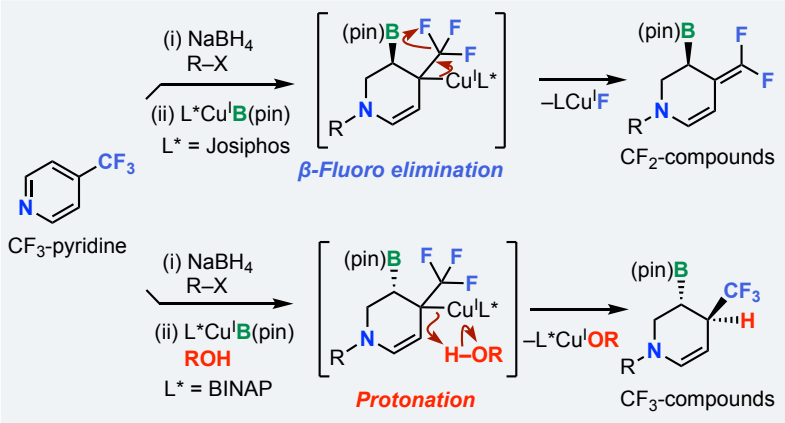

The efforts for synthesis of fluorine-containing organoboron compounds are another interest in my group, because these fluorine-containing organoboron compounds would become attractive synthons for an array of organofluorine compounds.[8] Since 2018, the author have reported the copper(I)-catalyzed enantioselective borylation reactions of allyltrifluorides and allyldifluorides using bis(pinacolato)diboron.[8a,b] These reactions presumably proceed through the enantioselective borylcupration of alkenes, followed by copper(I)-*β*-fluoro elimination to give *gem*-difluoroallylboronates (Scheme 1a).[8f]

***Scheme 2.*** The copper(I)-catalyzed enantioselective γ-borylsubstitution of allyltrifluoride via β-fluoroelimination




Based on these my group studies, the author anticipated the enantioselective borylation of readily available $CF_3$-substituted pyridine would be feasible for the synthesis of chiral fluorine-containing *N*-heterocyclic organoboronates. Herein, the author achieved the separately synthesis of chiral $CF_2$-containing *N*-heterocyclic organoboronates and chiral $CF_3$-containing *N*-heterocyclic organoboronates from 4-$CF_3$-pyridine with copper(I)/chiral phosphine catalysis. The $CF_2$-containing *N*-heterocyclic organoboronates that can conduct allylation with aldehyde was able to be obtained via β-fluoroelimination after the partial reduction of $CF_3$-pyridine. As the counterpart, the $CF_3$-containing *N*-heterocyclic organoboronates was able to be obtained via protoborylation with proton source after the partial reduction of $CF_3$-pyridiene. The derivatization of these compounds afforded the several fluorine-containing *N*-heterocyclic compounds, including fluorinated analogue of chiral bioactive compounds

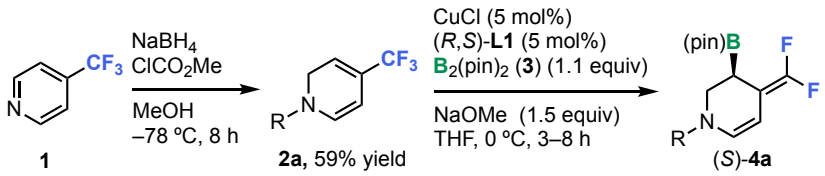
***Scheme 3.*** This work: separately synthesis of chiral $CF_2$-containing *N*-heterocyclic organoboronates and chiral $CF_3$-containing *N*-heterocyclic organoboronates.



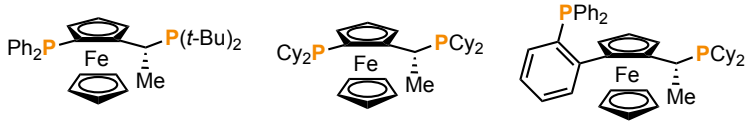

## Results and Discussion

First, the author began by searching for optimal conditions toward the synthesis of $CF_2$-containing *N*-heterocyclic boronates via β-fluoroelimination, and revealed that the reaction of methoxycarbonyl-protected 1,2-dihydropyridine **2a**, which was isolated from 4-$CF_3$-pyridine **1** using partial reduction method,[9] with bis(pinacolato)diboron (**3**) in the presence of CuCl/(R,S)-Josiphos **L1** (5 mol%), NaOMe (1.5 equiv) in THF at 0 ºC (Table 1, entry 1) afforded a chiral *N*-heterocyclic boronate bearing difluoro diene moiety. The, I also evaluated the other reaction parameters under the optimal conditions. Increasing the temperature up to r.t. resulted in slighly decreasing of yield and enantioselectivity (Table 1, entry 2) Using other chiral phosphine ligands such as (*R*,*S*)-Josiphos **L2**, (*R*,*S*)-Walphos **L3** at r.t. gave the products with moderate enantioselectivity (Table 1, entries 3, 4), whereas using (*R*)-BenzP* **L4**, (*R*,*R*)-BDPP **L5**, and (*R*)-BINAP **L6** result in drastically decreasing of the enantioselectivity (Table 1, entries 5–7). The nature of the bases was also found to have a marked impact on the reactivity (Table 1, entries 6–8). For example, the use of Na(O-*t*-Bu) resulted in a slight change in reactivity, whereas the use of other bases such as Li(O-*t*-Bu) led to a considerable decrease in reactivity (Table 1, entries 9, 10). Changing the solvent from THF to $Et_2O$ or 1,4-dioxane provided no improvement with respect to the yields and enantioselectivities (Table 1, entries 11, 12). Notably, in the absence of the copper catalyst, the reaction did virtually not proceed, which indicates that the copper catalyst is essential for this reaction (Table 1, entry 13). Use of a catalytic amount of NaOMe resulted in almost no reaction, which indicated that a stoichiometric amount of base was necessary to proceed the β-fluoroelimination. (Table 1, entry 14).[8f]

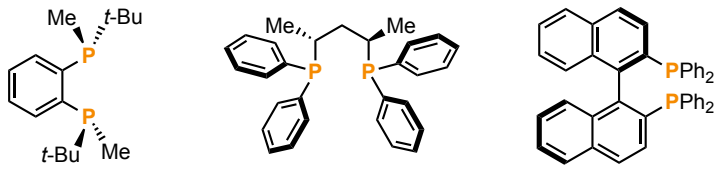
***Table 1.*** Optimization of the reaction conditions for chiral $CF_2$-containing N-heterocyclic organoboronates via β-fluoroelimination[a]




| Entry | Ligand | Deviation from standard conditions | Time (h) | Yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|
| 1 | (*R*,*S*)-**L1** | none | 8 | 88 | 98 |
| 2 | (*R*,*S*)-**L1** | r.t. | 3 | 79 | 85 |
| 3 | (*R*,*S*)-**L2** | r.t. | 5 | 71 | 68 |
| 4 | (*R*,*S*)-**L3** | r.t. | 5 | 88 | 15 |
| 5 | (*R*,*S*)-**L4** | r.t. | 8 | trace | – |
| 6 | (*R*,*S*)-**L5** | r.t. | 2 | 64 | 54 |
| 7 | (*R*)-**L6** | r.t. | 5 | 72 | 22 |
| 8 | (*R*,*S*)-**L1** | –20 °C | 8 | 47 | 95 |
| 9 | (*R*,*S*)-**L1** | Na(O-*t*-Bu) as base | 24 | 24 | 84 |
| 10 | (*R*,*S*)-**L1** | Li(O-*t*-Bu) as base | 24 | trace | – |
| 11 | (*R*,*S*)-**L1** | $Et_2O$ as solvent | 24 | 52 | 11 |
| 12 | (*R*,*S*)-**L1** | 1,4-dioxane as solvent | 24 | 73 | 90 |
| 13 | (*R*,*S*)-**L1** | no Cu cat. | 24 | trace | – |
| 14 | (*R*,*S*)-**L1** | 10 mol% of NaOMe | 24 | trace | – |




(*R*,*S*)-**L1** (*R*,*S*)-**L2** (*R*,*S*)-**L3**

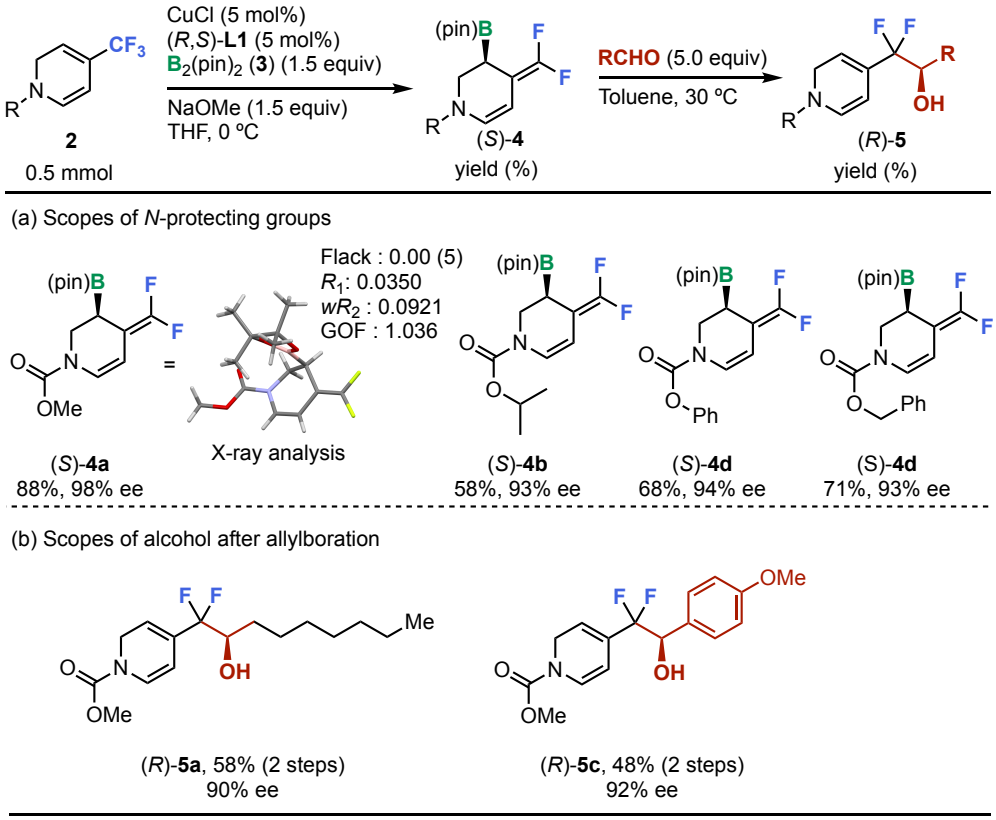



(*R*,*R*)-**L4** (*R*,*R*)-**L5** (*R*)-**L6**

[a]Best conditions: **2a** (0.25 mmol), CuCl (0.0125 mmol), ligand (0.0125 mmol), base (0.375 mmol), **2** (0.375 mmol) in THF (500 μL). [b]Determined by $^{19}F$ NMR analysis of the crude mixture with a fluorobenzene as an internal standard. [c]Determined by HPLC analysis of the corresponding alcohol.

Next, the optimized conditions were used to evaluate the scope of protecting groups (Table 2). The reactions of $CF_3$-substituted 1,2-dihydropyridines bearing various carbamate-type protecting groups such as *i*Pr, Ph, or Benzyl group in the presence of the Cu(I)/(*R*,*S*)-Josiphos **L1** catalyst system proceeded to give the desired products (*S*)-**4b**, (*S*)-**4c** and (*S*)-**4d** in good yield with high enantioselectivity (Table 2a). Notably, the absolute configuration of these compounds was determined according to the X-ray crystallographic analysis of the compounds (S)-**4a.** Next, the resultant optically active $CF_2$-containing *N*-heterocyclic boronates contained allylboron structure, which thus can conduct the allylation reaction with some electrophiles (Table 2b).[10] The author found that the allylation reaction of (*S*)-**4a** with *n*-pentanal in toluene delivered the corresponding alcohol (*R*)-**5a** in moderate yield with retaining high enantioselectivity. In addition, 4-methoxy substituted benzaldehyde also react with (*S*)-**4a** to afford the corresponding alcohol (*R*)-**5b** through stereospecific allylation reaction. Further substrate scopes of allylation reaction with aldehydes are now under ongoing in my laboratory.

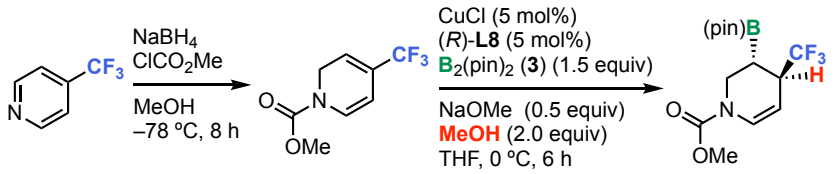
***Table 2.*** Scopes of protecting groups and alcohol allylation reactions with aldehydes[a]




[a]Same conditions as in entry 1 of Table 1.

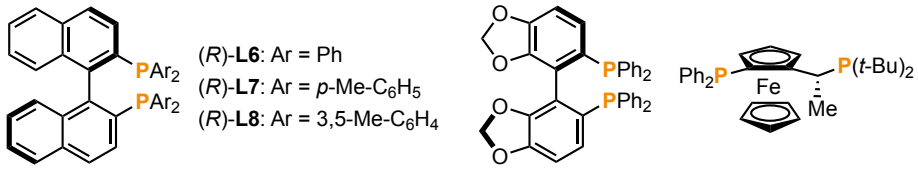
The author then turned the attention for optimization of the reaction conditions for chiral $CF_3$-containing *N*-heterocyclic organoboronates via protoborylation reaction of $CF_3$-substituted 1,2-dihydropyridine. As a result, the author found that the use of MeOH (2.0 equiv) with chiral phosphine ligand **L8** and catalytic amount of NaOMe (0.5 equiv) at 0 ºC gave the $CF_3$-containing protoborylation product in almost quantitatively yield with excellent enantioselectivity (Table 3, entry 1) and diastereoselectivity. In addition, the use of other BINAP ligands (*R*)-**L6** and (*R*)-**L7** as well as that of SEGPhos ligand (*R*)-**L9** gave the products quantitatively with slightly decrease the enantioselectivities (Table 3, entries 2–4). Importantly, the use of (*R*,*S*)-L1, which is the best ligand for the synthesis of (*S*)-**4** via β-fluoroelimination, deliverd the product in lower yield and enantioselectivity compared to that of BINAP type ligand (Table 3, entry 5). The use of stoichiometric base led to decrease the yield of protoborylation products due to induction of β-fluoroelimination by the effect of base (Table 3, entry 6). Further, changing other reaction parameter such as changing alcohol or base resulted in no improvement of the yield and enantioselectivity (Table 3, entries 7, 8).

***Table 3.*** Optimization of the reaction conditions for chiral $CF_3$-containing N-heterocyclic organoboronates via protoborylation[a]




**1a** **2a** (*R*,*R*)-**6a**

| Entry | Ligand | Deviation from standard conditions | Time (h) | Yield **6a** (%)[b] | ee **6a** (%)[c] | d.r.[c] |
|---|---|---|---|---|---|---|
| 1 | (*R*)-**L8** | none | 6 | quant. | 98 | >99:1 |
| 2 | (*R*)-**L6** | – | 6 | quant. | 86 | >99:1 |
| 3 | (*R*)-**L7** | – | 6 | quant. | 94 | >99:1 |
| 4 | (*R*)-**L9** | – | 18 | quant. | 70 | >99:1 |
| 5 | (*R*,*S*)-**L1** | – | 25 | 41 | –71 | >99:1 |
| 6 | (*R*)-**L9** | 1.5 eq. of NaOMe | 25 | 38 | 85 | >99:1 |
| 7 | (*R*)-**L9** | *i*-PrOH as alcohol | 24 | quant. | 62 | >99:1 |
| 8 | (*R*)-**L9** | K(O-*t*-Bu) as base | 6 | 85 | 83 | >99:1 |

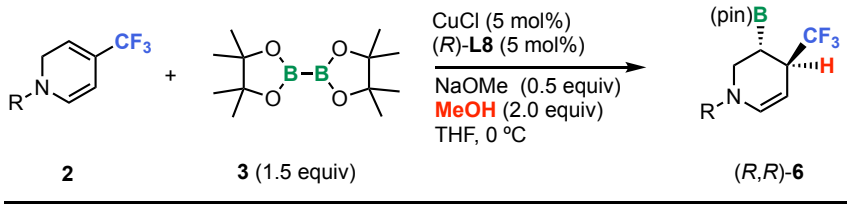



(*R*)-**L9** (*R*,*S*)-**L1**

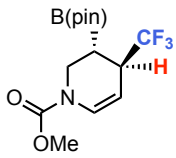
[a]Best conditions: **2a** (0.25 mmol), CuCl (0.0125 mmol), ligand (0.0125 mmol), base (0.125 mmol), **2** (0.375 mmol), MeOH (0.50 mmol) in THF (500 μL). [b]Determined by $^{19}$F NMR analysis of the crude mixture with a fluorobenzene as an internal standard. [c]Determined by HPLC analysis of the corresponding alcohol.

The optimized conditions for enantioselective protoborylation were used for further evaluation of the substrate scope (Table 4). Several carbamate protecting groups were tolerated for this reaction to deliver (*R*,*R*)-**6a**, **6b**, **6d** in high yields with excellent selectivities. The products (*R*,*R*)-**6c** was also obtained by the use of optimized conditions, where the absolute configuration was determined by X-ray crystallographic analysis.

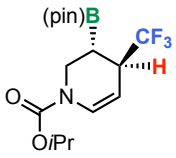
***Table 4.*** Scopes of protoborylation products[a]



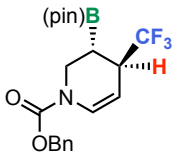

**2** **3** (1.5 equiv) (*R*,*R*)-**6**



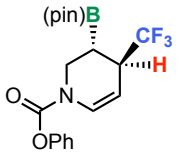

(*R*,*R*)-**6a**, 84%
98% ee, >95:5 d.r.




(*R*,*R*)-**6b**, 76%
98% ee, >95:5 d.r.

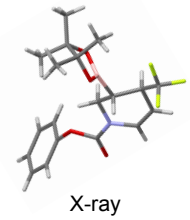



(*R*,*R*)-**6d**, 76%
98% ee, >95:5 d.r.




(*R*,*R*)-**6c**, 76%
96% ee, >95:5 d.r.

=



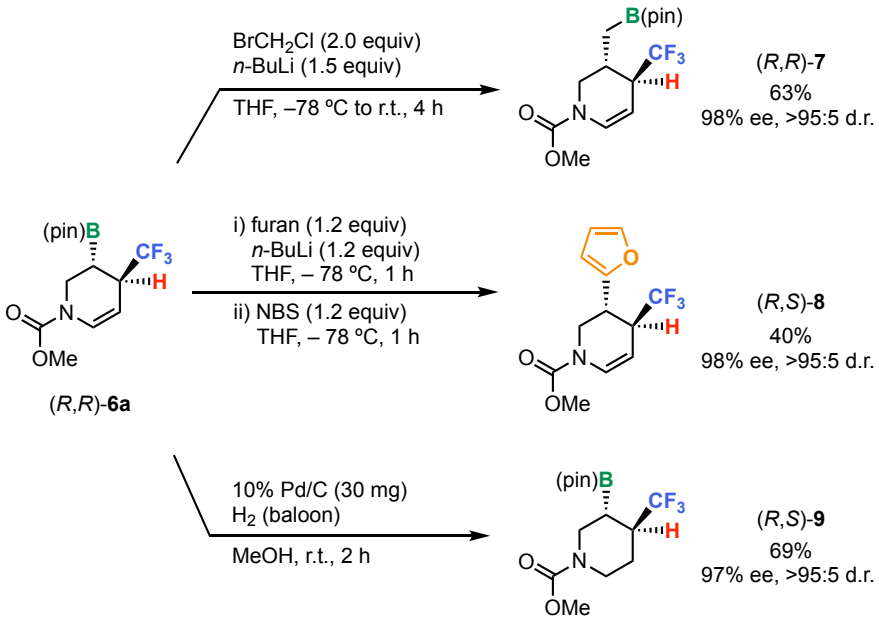
X-ray

Flack : 0.01(5)
$R_1$ : 0.0387, $wR_2$ : 0.1052
GOF : 1.098

[a]Same conditions as in entry 1 of Table 3.

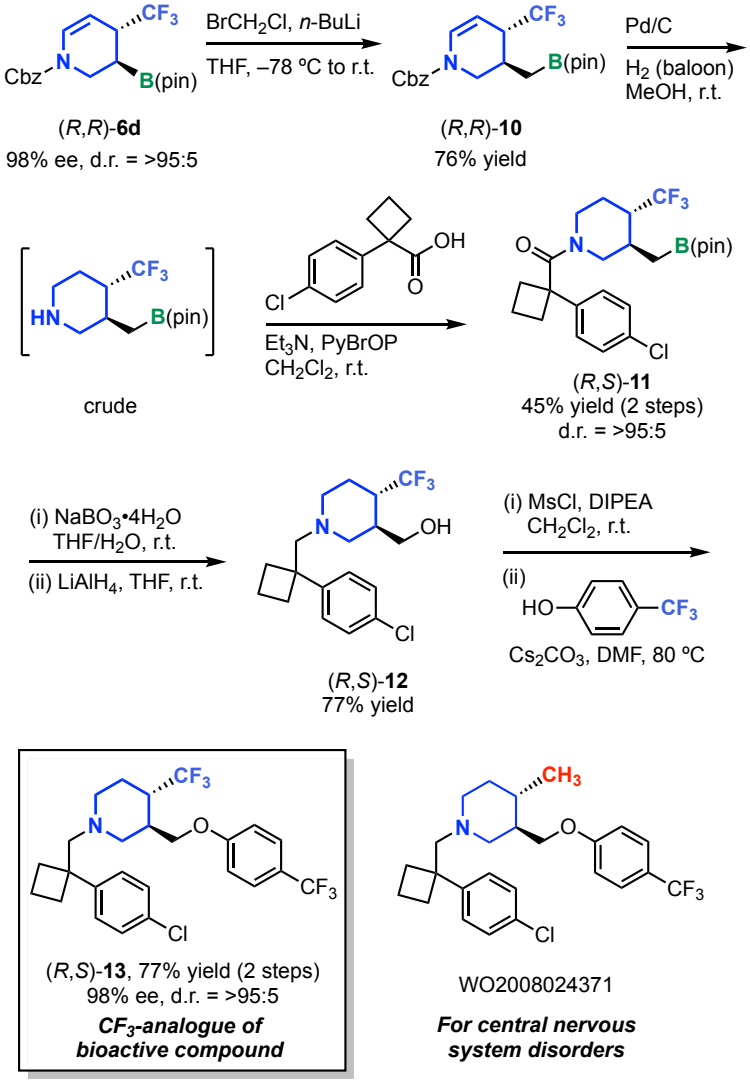
The transformations of the protoborylation reactions was conducted to demonstrate the utility of this protocol (Scheme 4). For example, the (*R*,*R*)-**6a** was subjected to a homologation with a halomethyl lithium reagent,[11] as well as an oxidative coupling with furan[12] to deliver several functionalized $CF_3$-containing *N*-heterocyclic compounds with high selectivities [(*R*,*R*)-**7** and (*R*,*S*)-**8**]. Further, the hydrogenation of (*R,R*)-**6a** gave (*R,S*)-**9** in good yield.

***Scheme 4***. Transformations



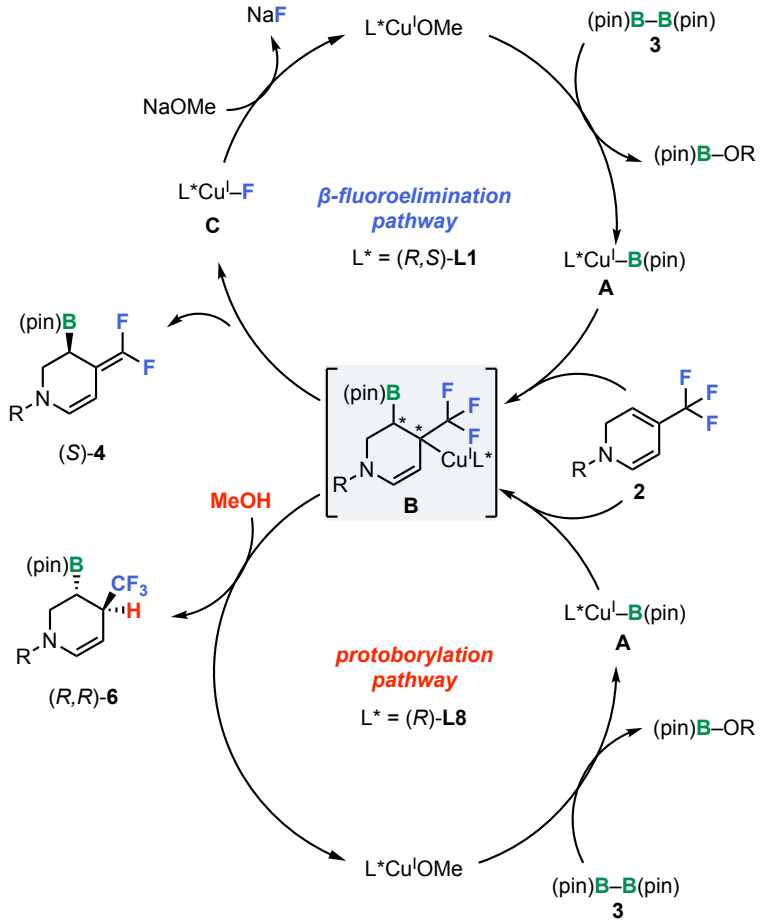

To demonstrate the utility of the products, I tried the synthesis of (*R*,*S*)-**13,** which would become the $CF_3$-analogue of bioactive compounds using the borylated product (*R*,*R*)-**6d** (Scheme 5).[13] Briefly, the boryl group in (*R*,*R*)-**6d** was successfully functionalized through a one carbon homologation reaction to deliver (*R*,*R*)-**10**.[11] Subsequent reduction by hydrogenation and condensation with carboxylic acid afforded the corresponding amide (*R*,*S*)-**11**, which was subjected to oxidation and reduction of a carbonyl group to give the (*R*,*S*)-**12**. Finally, the mesyl protection of alcohol and sequential etherification provided the $CF_3$-analogue of bioactive compounds (*R*,*S*)-**13** with high enantiomeric purity (98% ee).

***Scheme 5***. $CF_3$-analogue synthesis




Finally, we have proposed the reaction mechanism, depicted in Scheme 6. First, a copper(I) methoxide intermediate react with bis(pinacolato)diboron (**3**) to give boryl copper(I) intermediate **A**. Subsequent insertion of intermediate **A** toward the $CF_3$-substituted 1,2-dihydropyridine (**2**) could then result in the formation of allylcopper(I) intermediate B. From intermediate B, two possible pathways would proceed to afford $CF_2$-containing *N*-heterocyclic organoboronates (**4**) and $CF_3$-containing *N*-heterocyclic organoboronates (**6**) separately. For the $CF_2$-boronates, intermediate **B** would undergo β-fluoroelimination to generate the copper(I)-fluoride intermediate **C**, which then react with the stoichiometric amount of base to regenerate the copper(I) alkoxide intermediate and close the catalytic cycle. On the other hand, $CF_3$-boronates would be obtained via protonation of intermediate **B** and regenerate the copper(I) alkoxide intermediate.

***Scheme 6***. Proposed mechanism




## Conclusion

In summary of this chapter, the author developed a copper(I)-catalyzed enantioselective borylation reaction of $CF_3$-substituted 1,2-dihydropyridine, which is obtained through partial reduction of readily available 4-$CF_3$-pyridine, to afford the chiral fluorine-containing *N*-heterocyclic organoboronates. Notably, I synthesized chiral $CF_2$-containing *N*-heterocyclic organoboronates and chiral $CF_3$-containing *N*-heterocyclic organoboronates separately from same starting material by only changing of the reaction conditions. This novel protocol provided the versatile chiral fluorinated building blocks, which thus lead to easily access for bioactive chiral fluorine-containing *N*-heterocyclic compounds.

# Experiment

## 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). NMR spectra were recorded on JEOL JNM-ECX400P and JNM-ECS400 spectrometers ($^{1}$H: 392, 396, 400 and 401 MHz, $^{13}$C: 99 and 100 MHz and $^{19}$F: 373 MHz). Tetramethylsilane ($^{1}$H), $CDCl_3$ ($^{13}$C) and fluorobenzene ($^{19}$F, δ –113.60) were employed as the external standards, respectively. Fluorobenzene was used as an internal standard to determine NMR yield. Multiplicity was recorded as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. CuCl (ReagentPlus® grade, 224332-25G, ≥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. 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.

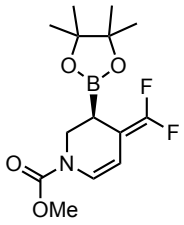
## Substrate Preparation

Methyl chloroformate (298.0 μL, 4.0 mmol) was added dropwise under nitrogen to a MeOH solution (10.0 mL) of $NaBH_4$ (151.3 mg, 4.0 mmol), 4-$CF_3$ pyridine (**1a**) (463.0 μL, 4.0 mmol) at −78 °C. The reaction was stirred at −78 °C for 2 h and then added additional methyl chloroformate (298.0 μL, 4.0 mmol) and the mixture was stirred at –78 ºC for 1 h. After the same addition protocol of chloroformate (298.0 μL, 4.0 mmol) and the mixture was stirred for 4 h, the reaction mixture was quenched by water. The mixture was extracted with $CH_2Cl_2$ three times. The combined organic layer was then dried over $MgSO_4$. After filtration, the solvents were removed by evaporation. The crude material was purified by flash silica gel column chromatography ($SiO_2$, EtOAc/hexane, 0:100–4:96) to give **2a** (492.8 mg, 2.4 mmol, 59%) as a clear liquid, which was immediately used in the next borylation reaction in order to prevent decomposition. Other 1,2-dihydropyridines **2b**–**2d** were prepared from the 4-$CF_3$ pyridine through the same procedures described above with different chloroformate, which were also immediately used in the next borylation reaction in order to prevent decomposition.

## General Borylation Procedure and Product Characterizations

**Procedure for methyl (*S*)-4-(difluoromethylene)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydropyridine-1(2*H*)-carboxylate [(*S*)-4a].**

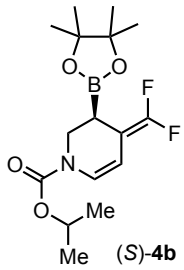
CuCl (2.6 mg, 0.026 mmol), (*R*,*S*)-**L1** (13.9 mg, 0.026 mmol) and bis(pinacolato)diboron (140.0 mg, 0.55 mmol) were placed in an oven-dried reaction vial. The vial was moved to an argon-filled glovebox. Dried NaOMe (40.5 mg, 0.75 mmol) was placed in a reaction vial. Then the vial was capped with a rubber septum and removed from the glovebox. Dry THF (1 mL) was added in the vial through the rubber septum using a syringe. **2a** (104.0 mg, 0.50 mmol) was added dropwise to the mixture at 0 °C. After stirring for 26 h at 0 ºC, 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 silica gel column chromatography ($SiO_2$, EtOAc/hexane, 0:100–8:92) to give the corresponding borylation product (*S*)-**4a** as a brown solid (58%, 91.9 mg, 0.29 mmol). The product contains a small amount of byproducts.



(*S*)-**4a**

$^1$H NMR (396 MHz, $CDCl_3$, δ): 1.19–1.23 (m, 12H), 2.28 (s, 1H), 3.32–3.48 (m, 1H), 3.78 (s, 3H), 4.04–4.14 (m, 1H), 5.45 (dd, *J* = 8.1, 35.4 Hz, 1H), 6.81 (dd, *J* = 7.9, 55.4 Hz, 1H).

**Isopropyl (*S*)-4-(difluoromethylene)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydropyridine-1(2*H*)-carboxylate [(*S*)-4b].**

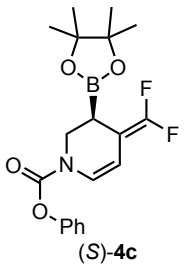


(*S*)-**4b**

The reaction was conducted with 117.9 mg (0.50 mmol) of **2b** for 24 h. The product (*S*)-**4b** was obtained in 83% yield (142.8 mg, 0.416 mmol). The product contains a small amount of byproducts.

$^1$H NMR (392 MHz, $CDCl_3$, δ): 1.20 (d, *J* = 3.1 Hz, 12H), 1.29 (d, *J* = 5.9 Hz, 6H), 2.27 (s, 1H), 3.34 (dd, *J* = 10.0, 45.7 Hz, 1H), 4.05–4.23 (m, 1H), 4.99 (septet, *J* = 6.3 Hz, 1H), 5.41 (dd, *J* = 7.4, 34.5 Hz, 1H), 6.82 (dd, *J* = 7.8, 48.6 Hz, 1H).

**Phenyl (*S*)-4-(difluoromethylene)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydropyridine-1(2*H*)-carboxylate [(*S*)-4c].**

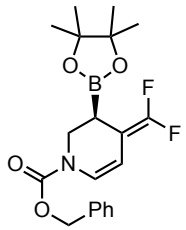


(*S*)-**4c**

The reaction was conducted with 134.8 mg (0.50 mmol) of **2c** for 24 h. The product (*S*)-**4c** was obtained in 68% yield (128.2 mg, 0.34 mmol). The product contains a small amount of byproducts.

$^1$H NMR (396 MHz, $CDCl_3$, δ): 1.21–1.25 (m, 12H), 2.36 (s, 1H), 3.45–3.55 (m, 1H), 4.17–4.45 (m, 1H), 5.56 (dd, *J* = 8.5, 24.8 Hz, 1H), 6.93 (dd, *J* = 7.9, 22.2 Hz, 1H), 7.09–7.17 (m, 2H), 7.19–7.27 (m, 1H), 7.34–7.41 (m, 1H).

**Benzyl (*S*)-4-(difluoromethylene)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydropyridine-1(2*H*)-carboxylate [(*S*)-4d].**



(*S*)-**4d**

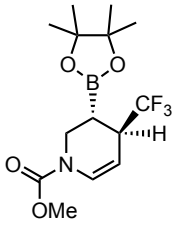
The reaction was conducted with 140.6 mg (0.50 mmol) of **2d** for 24 h. The product (*S*)-**4d** was obtained in 71% yield (138.8 mg, 0.355 mmol). The product contains a small amount of byproducts.

$^1$H NMR (392 MHz, $CDCl_3$, δ): 1.12–1.20 (m, 12H), 2.28 (s, 1H), 3.39 (ddd, *J* = 3.9, 12.5, 44.9 Hz, 1H), 4.06–4.31 (m, 1H), 5.10–5.32 (m, 2H), 5.45 (dd, *J* = 8.2, 42.3 Hz, 1H), 6.85 (dd, *J* = 8.6, 38.4 Hz, 1H), 7.29–7.43 (m, 5H).

**Procedure for methyl (3*R*,4*R*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)-3,4-dihydropyridine-1(2*H*)-carboxylate [(*R*,*R*)-6a].**

CuCl (2.5 mg, 0.025 mmol), (*R*)-**L8** (18.4 mg, 0.025 mmol) and bis(pinacolato)diboron (189.3 mg, 0.75 mmol) were placed in an oven-dried reaction vial. The vial was moved to an argon-filled glovebox. NaOMe (13.5 mg, 0.25 mmol) was placed in a reaction vial. Then the vial was capped with a rubber septum and removed from the glovebox. Dry THF (1 mL) was added in the vial through the rubber septum using a syringe. After **2a** (103.4 mg, 0.50 mmol) was added to the mixture at 0 ℃, MeOH (40.5 μL, 1.0 mmol) was added dropwise.

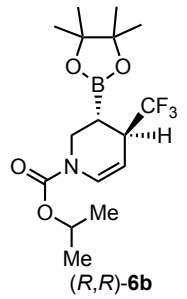
After stirring for 6 h at 0 ℃, the reaction mixture was passed through a short silica gel column (Φ: 10 mm, height of the silica-gel column: 30 mm) eluting with $Et_2O$. The crude material was purified by flash silica gel column chromatography ($SiO_2$, EtOAc/hexane, 0:100–9:91) to give the corresponding protoborylation product (*R*,*R*)-**6a** as a colorless oil (84%, 140.9 mg, 0.41 mmol).



(*R*,*R*)-**6a**

$^1$H NMR (396 MHz, $CDCl_3$, δ): 1.21 (d, *J* = 5.1 Hz, 12H), 1.63–1.71 (m, 1H), 3.00–3.12 (m, 1H), 3.57–3.83 (m, 2H), 3.78 (s, 3H), 4.99 (ddd, *J* = 3.7, 8.4, 39.9 Hz, 1H), 7.03 (dd, *J* = 8.7, 55.8 Hz, 1H).

**Isopropyl (3*R*,4*R*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)-3,4-dihydropyridine-1(2*H*)-carboxylate [(*R*,*R*)-6b].**

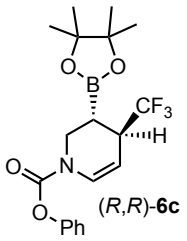


(*R*,*R*)-**6b**

The reaction was conducted with 117.6 mg (0.50 mmol) of **2b** for 6 h. The product (*R*,*R*)-**6b** was obtained in 76% yield (137.9 mg, 0.38 mmol).

$^1$H NMR (396 MHz, $CDCl_3$, δ): 1.21 (d, *J* = 4.8 Hz, 12H), 1.25–1.32 (m, 6H), 1.62–1.73 (m, 1H), 2.98–3.12 (m, 1H), 3.45–3.92 (m, 2H), 4.72–4.92 (m, 1H), 4.99 (septet, *J* = 6.3 Hz, 1H), 7.05 (dd, *J* = 8.3, 49.9 Hz, 1H).

**phenyl (3*R*,4*R*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)-3,4-dihydropyridine-1(2*H*)-carboxylate [(*R*,*R*)-6c].**

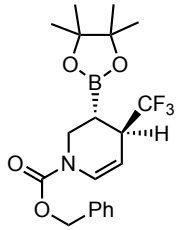


(*R*,*R*)-**6c**

The reaction was conducted with 134.6 mg (0.50 mmol) of **2c** for 6 h. The product (*R*,*R*)-**6c** was obtained in 76% yield (151.4 mg, 0.38 mmol).

$^1$H NMR (396 MHz, $CDCl_3$, *indicates a signal of the rotamer, δ): 1.24 (d, *J* = 2.0 Hz, 12H), 1.72–1.83 (m, 1H), 3.06–3.18 (m, 1H), 3.73–3.86 (m, 1.49H), *4.08 (dd, *J* = 5.7, 12.5 Hz, 0.47H), 4.98 (ddd, *J* = 3.9, 8.6, 31.0 Hz, 1H), 7.13 (t, *J* = 8.5 Hz, 2H), 7.18–7.26 (m, 2H), 7.38 (td, *J* = 2.6, 7.8 Hz, 2H).

**Benzyl (3*R*,4*R*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)-3,4-dihydropyridine-1(2*H*)-carboxylate [(*R*,*R*)-6d].**

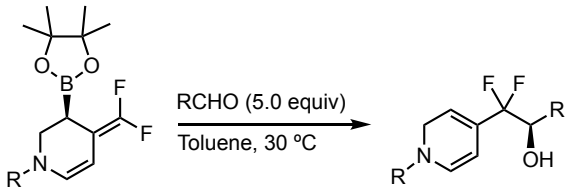



(*R*,*R*)-**6d**

The reaction was conducted with 141.7 mg (0.50 mmol) of **2d** for 6 h. The product (*R*,*R*)-**6d** was obtained in 76% yield (156.8 mg, 0.38 mmol).

$^1$H NMR (396 MHz, $CDCl_3$, δ): 1.13–1.23 (m, 12H), 1.64–1.75 (m, 1H), 3.00–3.12 (m, 1H), 3.53–3.98 (m, 2H), 4.87 (dq, *J* = 4.2, 49.7 Hz, 1H), 5.18 (t, *J* = 11.5 Hz, 1H), 5.22 (dt, *J* = 13.3, 39.3 Hz, 1H), 7.07 (dd, *J* = 8.1, 41.4 Hz, 1H), 7.30–7.43 (m, 5H).

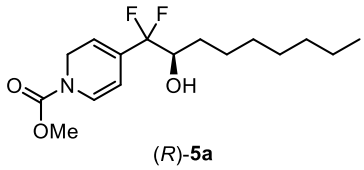
## Arylation Reaction Procedure and Product Characterizations




(*S*)-**4** (*R*)-**5**

**Procedure for methyl (*R*)-4-(1,1-difluoro-2-hydroxynonyl)pyridine-1(2*H*)-carboxylate [(*R*)-5a].**

Borylation product (*S*)-**4a** was submitted to the subsequent allylboration reaction without further purification. In a reaction vial, the crude material of (*S*)-**4a** (from 0.50 mmol **2a**) was dissolved in toluene (1 mL) at room temperature. After 1-octanal (389 μL, 2.50 mmol) was added to this solution and stirred 24 h. The reaction mixture was quenched by $CH_2Cl_2$ solution of triethanolamine (10% v/v, 3.0 mL) at room temperature. The mixture was separated with water and EtOAc, and then extracted three times with EtOAc. The combined organic layer was dried over $MgSO_4$, filtered and evaporated. The crude material was purified by flash silica gel column chromatography ($SiO_2$, EtOAc/hexane, 0:100–12:88) to give the corresponding protoborylation product (*R*)-**5a** as a colorless oil (58% (2 steps), 93.0 mg, 0.29 mmol).

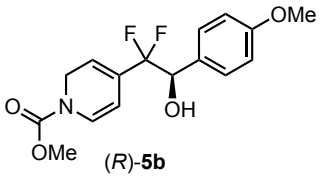



(*R*)-**5a**

$^1$H NMR (396 MHz, $CDCl_3$, δ): 0.88 (t, *J* = 6.7 Hz, 3H), 1.19–1.41 (m, 10H), 1.41–1.51 (m, 2H),

1.82–1.90 (m, 1H), 3.71–3.83 (m, 2H), 4.47 (s, 2H), 5.16–5.29 (m, 1H), 5.77 (d, *J* = 21.8 Hz, 1H), 6.81 (dd, *J* = 7.5, 49.9 Hz, 1H).

**Methyl (*R*)-4-(1,1-difluoro-2-hydroxy-2-(4-methoxyphenyl)ethyl)pyridine-1(2*H*)-carboxylate [(*R*)-4b].**

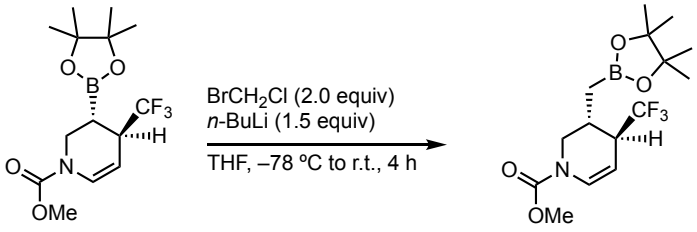


(*R*)-**5b**

The reaction was conducted with the crude material of (*S*)-**4a** (from 0.50 mmol **2a**) for 24 h. The product (*R*)-**5b** was obtained in 55% yield (90.5 mg, 0.278 mmol).

$^1$H NMR (396 MHz, $CDCl_3$, δ): 2.50 (d, *J* = 3.2 Hz, 1H), 3.78 (s, 3H), 3.81 (s, 3H), 4.36 (s, 2H), 4.85 (td, *J* = 3.7, 10.4 Hz, 1H), 5.04 (dd, *J* = 7.7, 23.2 Hz, 1H), 5.53 (d, *J* = 21.0 Hz, 1H), 6.71 (dd, *J* = 7.9, 50.3 Hz, 1H), 6.84–6.91 (m, 2H), 7.31 (d, *J* = 8.7 Hz, 2H).

## Homologation Reaction Procedure and Product Characterization[11]

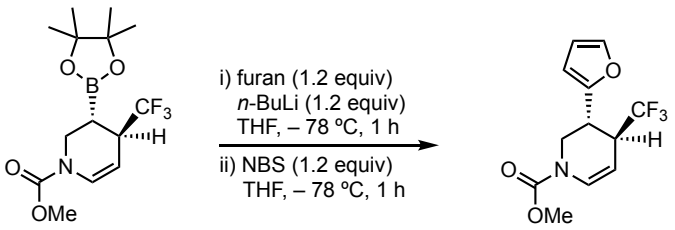


(*R*,*R*)-**6a** (*R*,*R*)-**7**

The one-carbon homologation was performed according to the literature procedure.[11] In an oven-dried reaction vial, (*R*,*R*)-**6a** (33.3 mg, 0.099 mmol) and bromochloromethane (13.4 μL, 0.20 mmol) were dissolved in dry THF (800 μL) in a nitrogen atmosphere. After the mixture was cooled to –78 °C, *n*-BuLi in hexane (1.64 M, 93.8 μL, 0.15 mmol) was added dropwise. The mixture was stirred at –78 °C for 30 min, and then stirred at room temperature for 3 h. The reaction mixture was quenched by the addition of aqueous $NH_4Cl$, extracted three times with $CH_2Cl_2$, dried over $MgSO_4$, and filtered. The crude material was purified by flash column chromatography ($SiO_2$, EtOAc/hexane, 0:100–8:92 to give the homologation product (*R*,*R*)-**7** (22.0 mg, 0.063 mmol, 63%) as a colorless oil.

$^1$H NMR (396 MHz, $CDCl_3$, δ): 0.90 (d, *J* = 6.3 Hz, 2H), 1.25 (s, 12H), 2.31–2.44 (m, 1H), 2.56–2.69 (m, 1H), 3.43 (t, *J* = 10.9 Hz, 1H), 3.60–3.72 (m, 1H), 3.77 (s, 3H), 4.77 (dq, *J* = 3.9, 38.3 Hz, 1H), 7.05 (dd, *J* = 7.7, 58.4 Hz, 1H).

## Oxidative Cross-Coupling Procedure and Product Characterization[12]

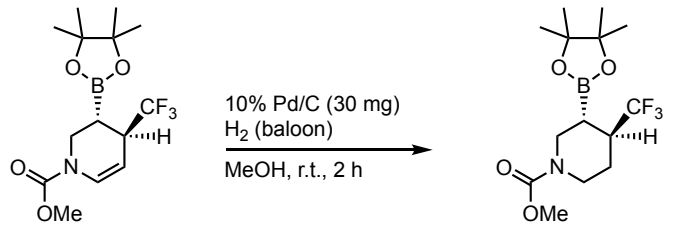



(*R*,*R*)-**6a** (*R*,*S*)-**8**

The Oxidative Cross-Coupling was performed according to the literature procedure.[12] Furan (8.7 μL, 0.12 mmol) were dissolved in THF (400 μL) under a nitrogen atmosphere. After the mixture was cooled to –78 °C, *n*-BuLi in hexane (1.64 M, 75.0 μL, 0.12 mmol) was added dropwise. The cooling bath was removed and the mixture was stirred at room temperature for 2 h. The mixture was cooled to –78 °C and (*R,R*)-**6a** (33.5 mg, 0.10 mmol) was added dropwise as a solution in THF (200 μL). After the mixture was stirred at –78 °C for 2 h, a solution of NBS (21.4 mg, 0.12 mmol) in THF (400 μL) was added dropwise. The mixture was stirred at –78 °C for 1 h. The reaction mixture was quenched by the addition of aqueous $Na_2S_2O_3$, extracted three times with $CH_2Cl_2$, dried over $MgSO_4$, filtered and concentrated under vacuum. The crude material was purified by flash column chromatography ($SiO_2$, EtOAc/hexane, 2:98–6:94 to give the homologation product (*R*,*S*)-**8** (11.0 mg, 0.040 mmol, 40%) as a colorless oil.

$^1$H NMR (396 MHz, $CDCl_3$, δ): 3.19–3.33 (m, 1H), 3.44 (s, 1H), 3.73 (dd, *J* = 3.4, 13.3 Hz, 1H), 3.78 (s, 3H), 3.88–4.07 (m, 1H), 4.80–4.98 (m, 1H), 6.11 (d, *J* = 2.8 Hz, 1H), 6.30 (q, *J* = 1.6 Hz, 1H), 6.98–7.20 (m, 1H), 7.33 (dd, *J* = 1.0, 1.8Hz, 1H).

## Hydrogenation Procedure and Product Characterization



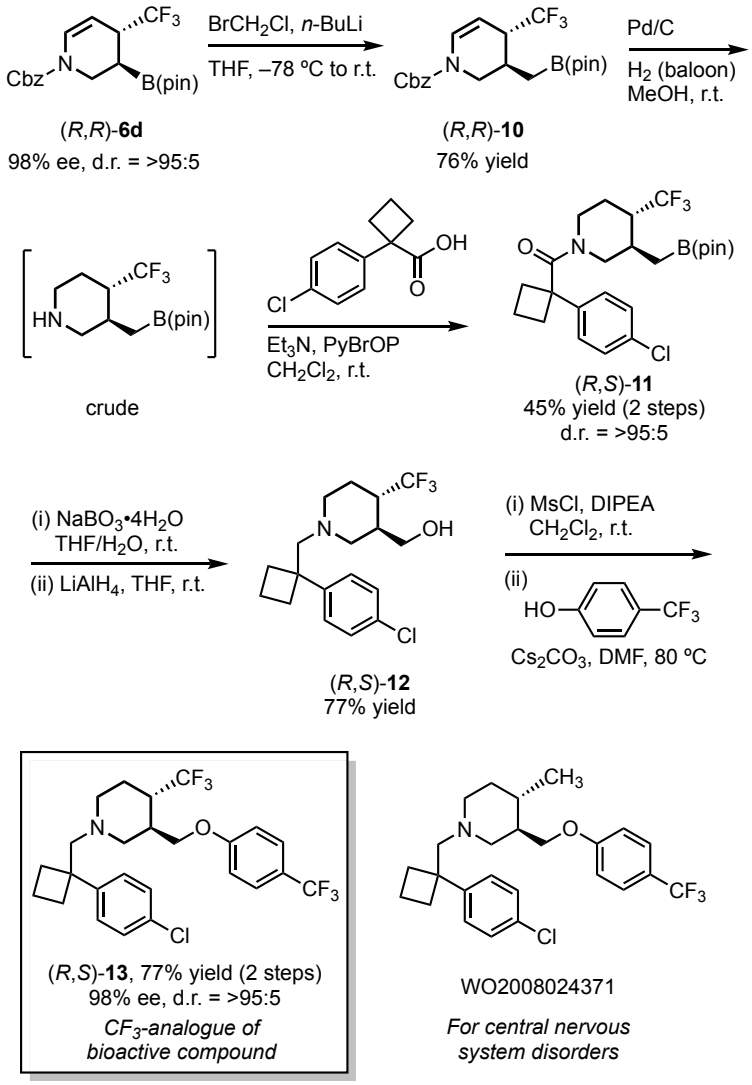

(*R*,*R*)-**6a** (*R*,*S*)-**9**

The boronate (*R*,*R*)-**6a** (34.1 mg, 0.102 mmol) and Pd/C (30.0 mg, 10%) were dissolved in MeOH (1.0 mL) under a nitrogen atmosphere. Hydrogen gas was then introduced to the reaction

mixture. After being stirred for 2 h, the mixture was filterd through short pad of celite with EtOAc as an eluent. The solvent was removed by evaporation under reduce pressure. The crude material was purified by flash column chromatography ($SiO_2$, EtOAc/hexane, 0:100–12:88 to give the homologation product (*R*,*S*)-**9** (23.5 mg, 0.0697 mmol, 69%) as a colorless oil.

$^1$H NMR (396 MHz, $CDCl_3$, δ): 1.18–1.32 (m, 13H), 1.50 (qd, *J* = 3.5, 12.3 Hz, 1H), 1.86 (dq, *J* = 3.2, 13.2 Hz, 1H), 2.30–2.46 (m, 1H), 2.70–2.94 (m, 1H), 3.70 (s, 3H), 3.96–4.31 (m, 2H).

## Procedure for the Synthesis of $CF_3$-Analogue of Bioactive Compounds (*R*,*S*)-13




The one-carbon homologation was performed according to the literature procedure.[11] In an oven-dried reaction vial, (*R,R*)-**6d** (617.2 mg, 1.5 mmol) and bromochloromethane (201.1 µl, 3.0 mmol) were dissolved in dry THF (8.0 mL) in a nitrogen atmosphere. After the mixture was cooled to – 78 °C, *n*-BuLi in hexane (1.64 M, 1.4 mL, 2.25 mmol) was added dropwise. The mixture was stirred at –78 °C for 30 min, and then stirred at room temperature for 3 h. The reaction mixture was quenched by the addition of aqueous $NH_4Cl$, extracted three times with $CH_2Cl_2$, dried over $MgSO_4$, and filtered. The crude material was purified by flash column chromatography ($SiO_2$, EtOAc/hexane, 0:100–16:84) to give the homologation product (*R*,*R*)-**10** (503.5 mg, 1.2 mmol, 79%) as a colorless oil.

The boronate (*R*,*R*)-**10** (503.5 mg, 0.12 mmol) and Pd/C (40.0 mg, 10%) were dissolved in MeOH (3.5 mL) under a nitrogen atmosphere. Hydrogen gas was then introduced to the reaction mixture. After being stirred for 2 h, the mixture was filterd through short pad of celite

with EtOAc as an eluent. The solvent was removed by evaporation under reduce pressure. The resulting crude material was used in the next reaction without further purification.

In an oven-dried reaction vial, 1-(4-chlorophenyl)cyclobutane-1-carboxylic (372.9 mg, 1.77 mmol) and PyBrOP (852.7 mg, 1.83 mmol) were dissolved in dry $CH_2Cl_2$ (5 mL) under a nitrogen atmosphere. The crude material in dry $CH_2Cl_2$ (4.0 mL) was then added to the reaction mixture at r.t. After being stirred for 17 h, the reaction mixture was quenched by the addition of aqueous $NaHCO_3$, extracted three times with $CH_2Cl_2$, dried over $MgSO_4$, and filtered. The crude material was purified by flash column chromatography ($SiO_2$, EtOAc/hexane, 0:100–22:78) to give the corresponding amide (*R*,*S*)-**11** (257.7 mg, 0.53 mmol, 45%, 2 steps) as a colorless oil.

In a reaction vial, the corresponding amide (*R*,*S*)-**11** (257.7 mg, 0.53 mmol) was dissolved in THF/$H_2O$ (1/1, 5.0 mL). $NaBO_3$•$4H_2O$ (402.5 mg, 2.65 mmol) was then added to the reaction mixture at room temperature. After being stirred for 3 h, the reaction mixture was extracted three times with $CH_2Cl_2$, dried over $MgSO_4$, and filtered. The resulting crude material was used in the next reaction without further purification.

In an oven-dried reaction vial, $LiAlH_4$ (372.9 mg, 1.77 mmol) was dissolved in dry THF (3.5 mL) under a nitrogen atmosphere. The crude material in dry THF (2.0 mL) was then added to the reaction mixture at 0 ºC. After being stirred at r.t for 3 h, the reaction mixture was carefully quenched by the addition of $H_2O$, then extracted four times with $CH_2Cl_2$, dried over $MgSO_4$, and filtered. The crude material was purified by flash column chromatography ($SiO_2$, EtOAc/hexane, 0:100–20:80) to give the corresponding alcohol (*R*,*S*)-**12** (148.4 mg, 0.53 mmol, 77%, 2 steps) as a colorless oil.

In an oven-dried reaction vial, alcohol (*R*,*S*)-**12** and DIPEA (180.8 µL, 1.06 mmol) were dissolved in dry $CH_2Cl_2$ (5.0 mL) under a nitrogen atmosphere. Methanesulfonyl chloride (47.4 µL, 0.61 mmol) was then added at 0 °C. After being stirred for 24 h at r.t., $H_2O$ was added to the reaction mixture. The mixture was then extracted three times with $CH_2Cl_2$, dried over $MgSO_4$, and filtered. The crude material was purified by flash column chromatography ($SiO_2$, $Et_2O$/hexane, 0:100–4:96) to give the corresponding mesylate (155.0 mg, 0.35 mmol, 86%) as a white solid. The diastereomeric ratio was determined by $^1$H NMR analysis.

In an oven-dried reaction vial, the mesylate (87.2 mg, 0.2 mmol), 4-(trifluoromethyl)phenol (34.0 mg, 0.21 mmol) and $Cs_2CO_3$ (195.5 mg, 0.6 mmol) were dissolved in dry DMF (2.0 mL) under a nitrogen atmosphere. After being stirred at 80 ºC for 2 h, the reaction mixture was quenched by addition of $H_2O$. The mixture was then extracted three times with $Et_2O$, dried over $MgSO_4$, and filtered. The crude material was purified by flash column chromatography ($SiO_2$, $Et_2O$/hexane, 0:100–2:98) to give the $CF_3$-analogue of bioactive compound (*R*,*S*)-**13** (89.3 mg, 0.177 mmol, 89%) as a colorless oil. The diastereomeric ratio was determined by $^1$H NMR analysis.

$^{1}$H NMR (392 MHz, $CDCl_3$, δ): 1.48–1.64 (m, 1H), 1.72–1.91 (m, 2H), 1.95–2.33 (m, 9H), 2.47–2.57 (m, 2H), 2.64 (q, $J$ = 13.3 Hz, 2H), 3.76–3.93 (m, 2H), 6.86 (d, $J$ = 8.6 Hz, 2H), 7.08 (d, $J$ = 8.6 Hz, 2H), 7.24 (d, $J$ = 8.23 Hz, 2H), 7.53 (d, $J$ = 7.5 Hz, 2H). Daicel CHIRALPAK® IA-3, 2-PrOH/Hexane = 0.5/99.5, 0.5 mL/min, 40 ºC, (*R*,*S*)-isomer: $t_R$ = 10.18 min., (*S*,*R*)-isomer: $t_R$ = 10.97 min.

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(8) For selected examples of the synthesis of fluorine-containing organoboron compounds with copper(I)-catalysis, see; (a) Kojima, R.; Akiyama, S.; Ito, H. *Angew. Chem., Int. Ed.* **2018**, *57*, 7196. (b) Akiyama, S.; Kubota, K.; Mikus, M. S.; Paioti, P. H. S.; Romiti, F.; Liu, Q.; Zhou, Y.; Hoveyda, A. H.; Ito, H. *Angew. Chem., Int. Ed.* **2019**, *58*, 11998. (c) Akiyama, S.; Nomura, S.; Kubota, K.; Ito, H. *J. Org. Chem.* **2020**, 85, 4172. (d) Ito, H.; Seo, T.; Kojima, R.; Kubota, K. *Chem. Lett.* **2018**, *47*, 1330. (e) Gao, P.; Yuan, C.; Zhao, Y.; Shi, Z. *Chem* **2018**, *4*, 2201. (f) Paioti, P. H. S.; Del Pozo, J.; Mikus, M. S.; Lee, J.; Koh, M. J.; Romiti, F.; Torker, S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2019**, *141*, 19917.

(9) Foowler, F. W. *J. Org. Chem*. **1972**, *37*, 1321. The $CF_3$-substituted 1,2-dihydropyridines were isolated prior to the next borylation step, but should be used immediately in order to prevent

decomposition.
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(11) Sadhu, K. M.; Matteson, D. S. *Organometallics* **1985**, *4*, 1687.
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# Chapter4.

# Copper(I)-Catalyzed Radical Relay Enabling Intermolecular 1,2-Alkylborylation of Unactivated Olefins

## Abstract

The first catalytic intermolecular 1,2-alkylborylation reaction via a radical relay mechanism between unactivated olefins, bis(pinacolato)diboron, and an alkyl electrophile is reported. Successful implementation of this method requires that the competing boryl substitution of the alkyl electrophile is suppressed. This challenge was overcome using electronically or sterically demanding alkyl electrophiles, which results in the simultaneous, and highly regioselective, introduction of either a *gem*-difluoro alkyl group or a tertiary alkyl group and a boryl group across the C=C double bond.


## Introduction

The transition-metal-catalyzed radical-relay strategy for the intermolecular 1,2-carbofunctionalization of widely available unactivated olefins is one of the most useful protocols for rapidly constructing complex carbon-based structures (Figure 1). Only a catalytic amount of a radical-generating reagent is required[1,2] and typically, this process involves a single-electron transfer (SET) from an organometallic intermediate to an electrophile. Subsequent addition of the resulting radical to an olefin occurs with high regioselectivity and is followed by radical recombination.[3–5] One of the main advantages of this protocol is that it tolerates electronically or sterically demanding alkyl electrophiles that cannot be used in catalytic 1,2-carbofunctionalization reactions that involve $S_N2$-type nucleophilic substitutions.

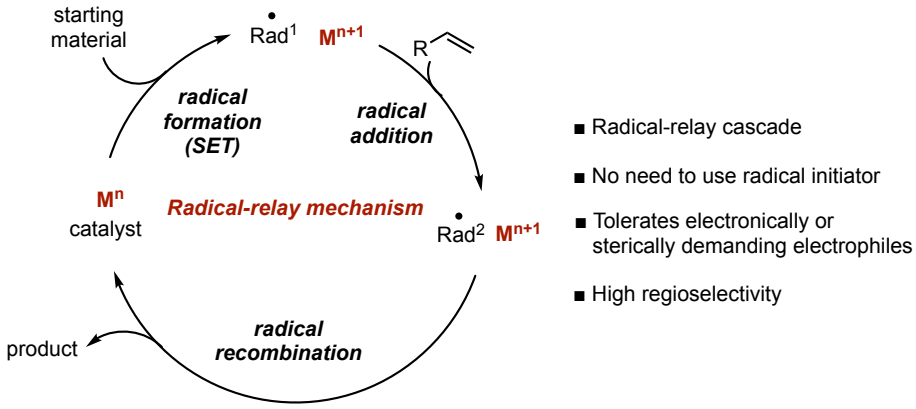
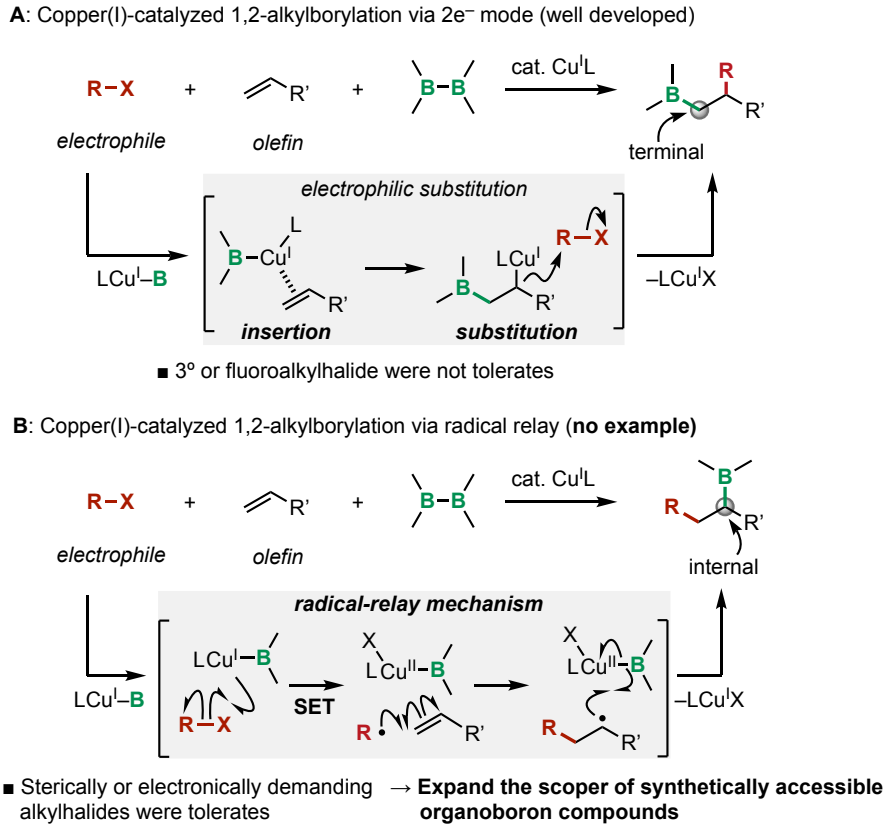



***Figure 1.*** The details of the radical-relay mechanism

Similarly, the intermolecular 1,2-carboborylation of olefins via a radical relay, a transformation that involves simultaneous installation of a C–C bond and a transformable C–B bond, would undoubtedly be highly attractive. This approach would expand the scope of synthetically accessible organoboron compounds that bear complex carbon frameworks.[6] Despite the significant progress that has been made in radical-relay chemistry, the intermolecular 1,2-carboborylation of olefins via a radical relay has not yet been reported.[7]

During the past decades, an array of copper(I)-catalyzed 1,2-alkylborylation reactions of olefins has been reported (Scheme 1).[6,8] In general, these reactions proceed via a two-electron mode, in which a borylcopper(I) intermediate reacts with an olefin followed by electrophilic substitution of the resulting alkylcopper(I) intermediate. A new C($sp^3$)–B bond and a new C($sp^3$)–C bond are simultaneously formed at the terminal and internal positions of the olefin, respectively (Scheme 1A).[8] In contrast, a radical-relay strategy would provide an alternative approach with reverse regioselectivity.[9] Ideally, this process would involve an SET from a borylcopper(I) intermediate to an alkyl electrophile. Radical addition of the resulting alkyl radical to an olefin, followed by C–B bond formation would simultaneously form a new C($sp^3$)–B bond at the internal position of the olefin and a new C($sp^3$)–C bond at the terminal position (Scheme 1B). This alternative pathway would present an opportunity to enable the divergent synthesis of organoboronates.



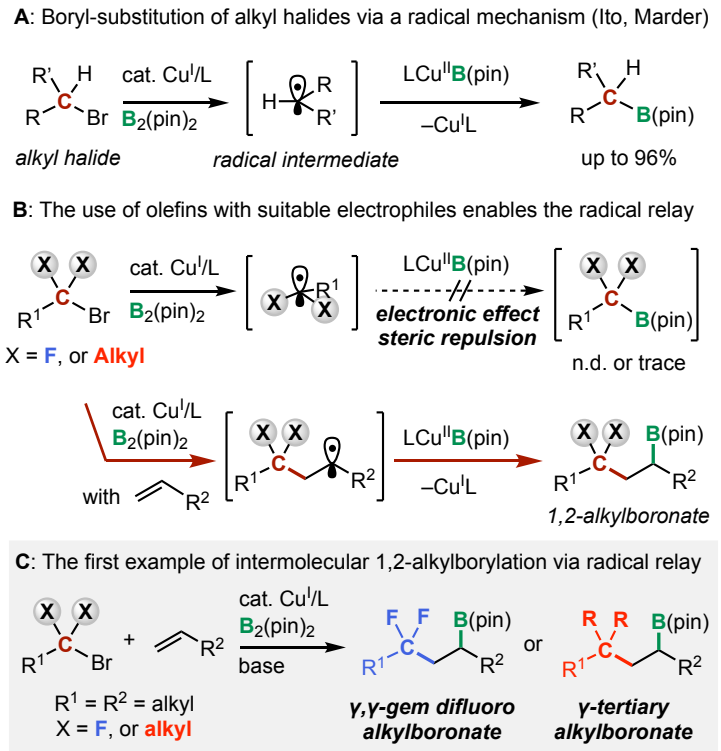

***Scheme 1.*** A method for copper(I)-catalyzed intermolecular 1,2-alkylborylation reactions.

In 2012, my group and that of Marder independently reported copper(I)-catalyzed boryl substitution reactions of alkyl halides with bis(pinacolato)diboron (Scheme 2A).[10] These reactions proceed via an SET from a borylcopper(I) intermediate to an alkyl halide, generating an alkyl radical, followed by radical recombination to form a C–B bond. The application of these reaction mechanisms for an intramolecular borylative radical cyclization was achieved in 2017.[9] Despite

this success, the intermolecular counterpart has not yet been achieved due to the difficulty in suppressing the direct coupling between the borylcopper(I) intermediate and the carbon electrophile. During related studies on the copper(I)-catalyzed borylation of alkyl halides, the author has encountered a problem where, despite observing consumption of the starting materials, substrates with electronically or sterically demanding substituents did not afford the desired boryl substitution products (Scheme 2B). I hypothesized that this outcome could be due to the boryl copper(II) intermediate being inaccessible to the alkyl radical intermediate on account of electronic effect or steric repulsion (Scheme 2B). Inspired by these results, I suspected that the reaction of an unactivated olefin with bis(pinacolato)diboron and an electronically or sterically demanding alkyl electrophile might offer an alternative pathway to enable the intermolecular 1,2-alkylborylation reaction.[10]

Herein, we report the first example of an intermolecular 1,2-alkylborylation of unactivated olefins via a radical-relay strategy (Scheme 2C). The key to the success of this protocol is the use of electronically or sterically demanding alkyl electrophiles, such as α,α-difluoro alkyl bromides or tertiary alkyl bromides, to suppress undesired boryl substitution reactions. Notably, the products in these reactions, γ,γ-*gem*-difluoro alkylboronates and γ-tertiary alkylboronates, are difficult to access via any other borylation approaches.[8]

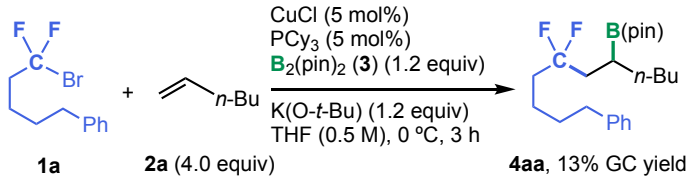
***Scheme 2.*** Synthetic strategy employed in this work



## Result and Discussion

As a proof-of-concept, I selected α,α-difluoro alkyl bromide **1a** as the alkyl electrophile; similar to our previously reported catalysts system, **1a** did not furnish the corresponding boryl substitution product.[9,10a] Surprisingly, the trial experiment delivered the desired 1,2-alkylborylation product (**4aa**) in 13% gas chromatography (GC) yield in the presence of CuCl/$PCy_3$, our efficient catalyst for the boryl substitution of alkyl halides, under concomitant formation of unidentified byproducts (Scheme 3).[9]

***Scheme 3.*** Initial attempt of 1,2-alkylborylation via radical relay



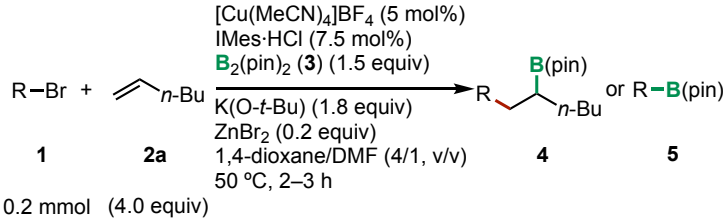

**1a** **2a** (4.0 equiv) **4aa**, 13% GC yield

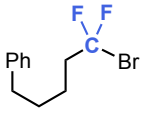
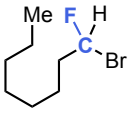
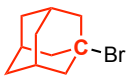
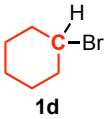
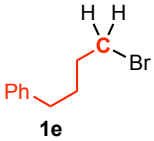
[a]Conditions; **1a** (0.1 mmol), **2a** (0.4 mmol), **3** (0.12 mmol), CuCl (0.005 mmol), $PCy_3$ (0.005 mmol), K(O-*t*-Bu) (0.12 mmol), THF (200 μL). The yield of **4aa** was determined by GC analysis of the crude reaction mixture with $C_{13}H_{28}$ as the internal standard.

This initial success prompted me to conduct an extensive optimization study of the reaction conditions.[11] I found that **4aa** could be obtained in a 79% GC yield using a $[Cu(MeCN)_4]BF_4$/IMes·HCl catalyst system with $B_2(pin)_2$, K(O-*t*-Bu), and a catalytic amount of $ZnBr_2$ as an additive in 1,4-dioxane/DMF (4/1, v/v) at 50 ºC (Table 1, entry 1). Using the optimized conditions, the author then investigated several other alkyl bromides to understand which electrophiles are suitable for the intermolecular 1,2-alkylborylation (Table 1, entries 2–5). Interestingly, although α,α-difluoro alkyl bromide did not give boryl-substitution product **5** under these reaction conditions, α-monofluoro alkyl bromide **1b** afforded the corresponding boryl-substitution product without the formation of the 1,2-alkylborylation product (Table 1, entry 2). These results indicate that the fluorine moieties play an essential role in preventing the boryl-substitution reaction through electronic effect and by facilitating the radical-relay mechanism efficiently. The reaction with 1-adamantyl bromide **1c**, a tertiary alkyl bromide, also delivered the 1,2-alkylborylation product in good yield, while boryl-substitution product **5** was not detected (Table 1, entry 3). In contrast, secondary (**1d**) or primary alkyl bromides (**1e**) predominantly furnished the boryl-substitution products with very little 1,2-alkylborylation product (Table 1, entries 4 and 5). These results suggest that steric hindrance around the C–X bond is another important factor to facilitate the radical relay efficiently. I also evaluated the other reaction parameters under the optimal conditions. Notably, the choice of ligand had a marked influence on

the product yields (Table 1, entries 6 and 7). Using ICy·HCl gave the desired product in moderate yield (Table 1, entry 6), while using a phosphine ligand such as $PCy_3$ resulted in the formation of a complex product mixture and decreased the yield (Table 1, entry 7). The effects of other parameters were also investigated (Table 1, entries 8–13). Decreasing the quantity of olefin slightly diminished the product yield of the target (Table 1, entries 8 and 9). Using THF as the solvent resulted in a similar outcome (Table 1, entry 10). Using other additives such as $MgBr_2$ is not crucial for the reaction (Table 1, entry 11) and, even though the product could be obtained without an additive, the yield drastically decreased to 20% (Table 1, entry 12).[12] In the absence of the copper catalyst, the reaction did virtually not proceed, which indicates that the copper catalyst is essential for this reaction (Table 1, entry 13). In all cases where **1a** was the electrophile, the simple boryl substitution product (**5**) was not detected.

***Table 1.*** Optimization of the reaction conditions[a]



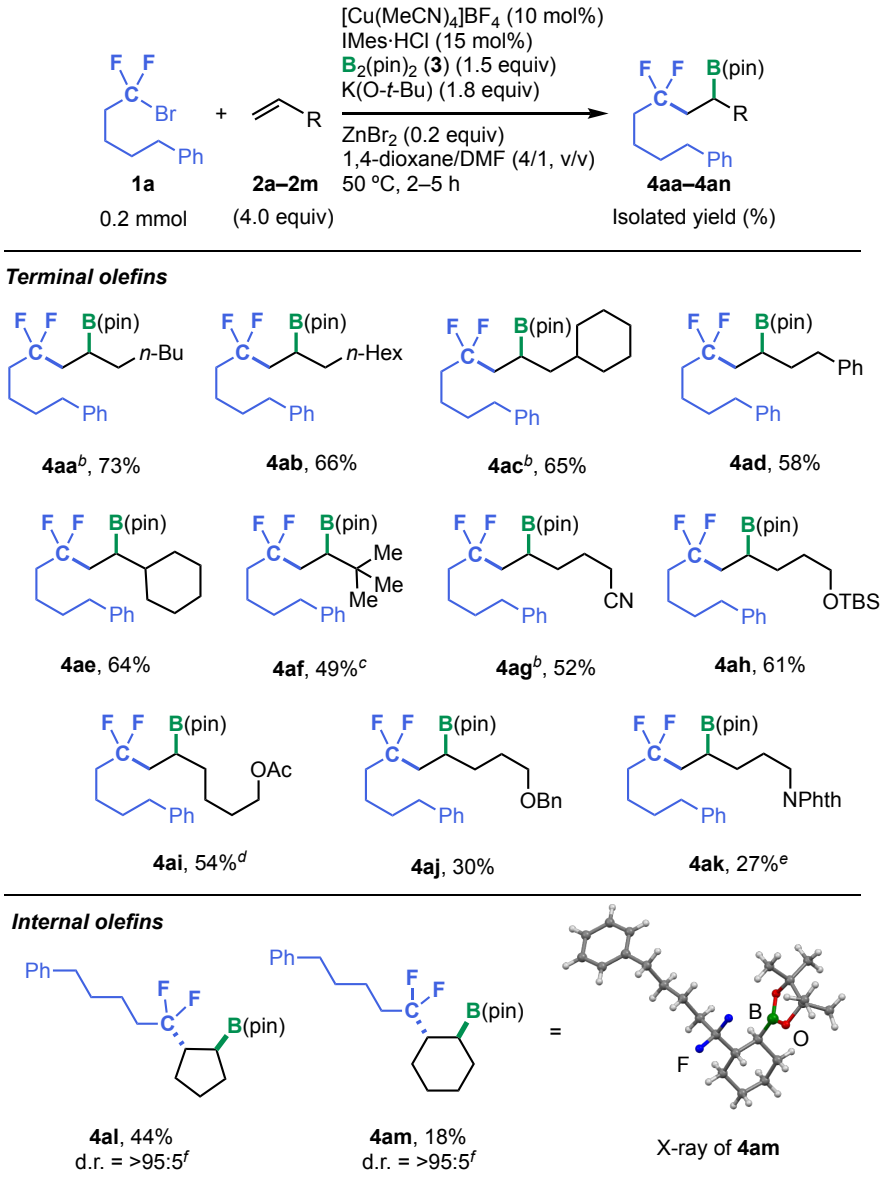

| Entry | Electrophile | Deviation from the standard conditions | Yield (%) | |
|---|---|---|---|---|
| | | | **4**[b] | **5**[d] |
| 1[c] |  **1a** | None | 79 (74)[d] | n.d. |
| 2[c] |  **1b** | – | n.d. | 52[e] |
| 3[c,f,g] |  **1c** | – | 71[d] | n.d. |
| 4[c,f] |  **1d** | – | trace | 60 |
| 5[c,f] |  **1e** | – | n.d. | 89 |
| 6 | **1a** | ICy·HCl as the ligand | 55 | n.d. |

| | | | | |
|---|---|---|---|---|
| 7 | **1a** | $PCy_3$ as the ligand | 11 | n.d. |
| 8 | **1a** | 3.0 eq. of the olefin | 73 | n.d. |
| 9 | **1a** | 2.0 eq. of the olefin | 58 | n.d. |
| 10 | **1a** | THF as the solvent | 49 | n.d. |
| 11 | **1a** | $MgBr_2$ instead of $ZnBr_2$ | 27 | n.d. |
| 12 | **1a** | No $ZnBr_2$ | 20 | n.d. |
| 13 | **1a** | No Cu cat. | trace | n.d. |

[a]Conditions: **1** (0.1 mmol), **2a** (0.4 mmol), **3** (0.15 mmol), $[Cu(MeCN)_4]BF_4$ (0.005 mmol), IMes·HCl (0.0075 mmol), K(O-*t*-Bu) (0.18 mmol), $ZnBr_2$ (0.02 mmol) in 1,4-dioxane (200 μL) and DMF (50 μL) (for details, see the Supporting Information). [b]Determined by GC analysis of the crude reaction mixture with $C_{13}H_{28}$ as the internal standard. [c]0.2 mmol scale. [d]Isolated yield. [e]Determined by $^{19}F$ NMR analysis with fluorobenzene as the internal standard. [f]10 mol% of Cu cat. and 15 mol% of IMes·HCl were used. [g]The ratio of 1,4-dioxane/DMF was 6/1 (v/v).

In addition to the above investigations, the author sought to explore the scope of the unactivated olefins in the reaction with α,α-difluoro alkyl bromide **1a** (Scheme 4). A wide range of unactivated terminal olefins furnished the corresponding γ,γ-*gem*-difluoro *α*-alkylboronates that bear either an *n*-butyl (**4aa**), *n*-hexyl (**4ab**), allyl cyclohexyl (**4ac**), or phenethyl (**4ad**) group in good yield. The more sterically hindered olefins also reacted under the optimal conditions to give products that bear cyclohexyl (**4ae**) and *t*-butyl (**4af**) groups, although the yield was slightly lower in these cases. Functional groups such as a cyano (**4ag**), a *t*-butyl dimethylsilyl ether (**4ah**), and an acetyl group (**4ai**), were tolerated in the position distal to the C=C double bond. The reactions with benzyl ether (**4aj**) and phthalimide (**4ak**) represent exceptions. Furthermore, the reaction of an internal strained olefin afforded the corresponding product (**4al**) in moderate yield with high diastereoselectivity. Moreover, the reaction with cyclohexene furnished **4am** in low yield. The relative stereochemistry of **4am** was determined by X-ray crystallography.

***Scheme 4.*** Scopes of olefins[a]

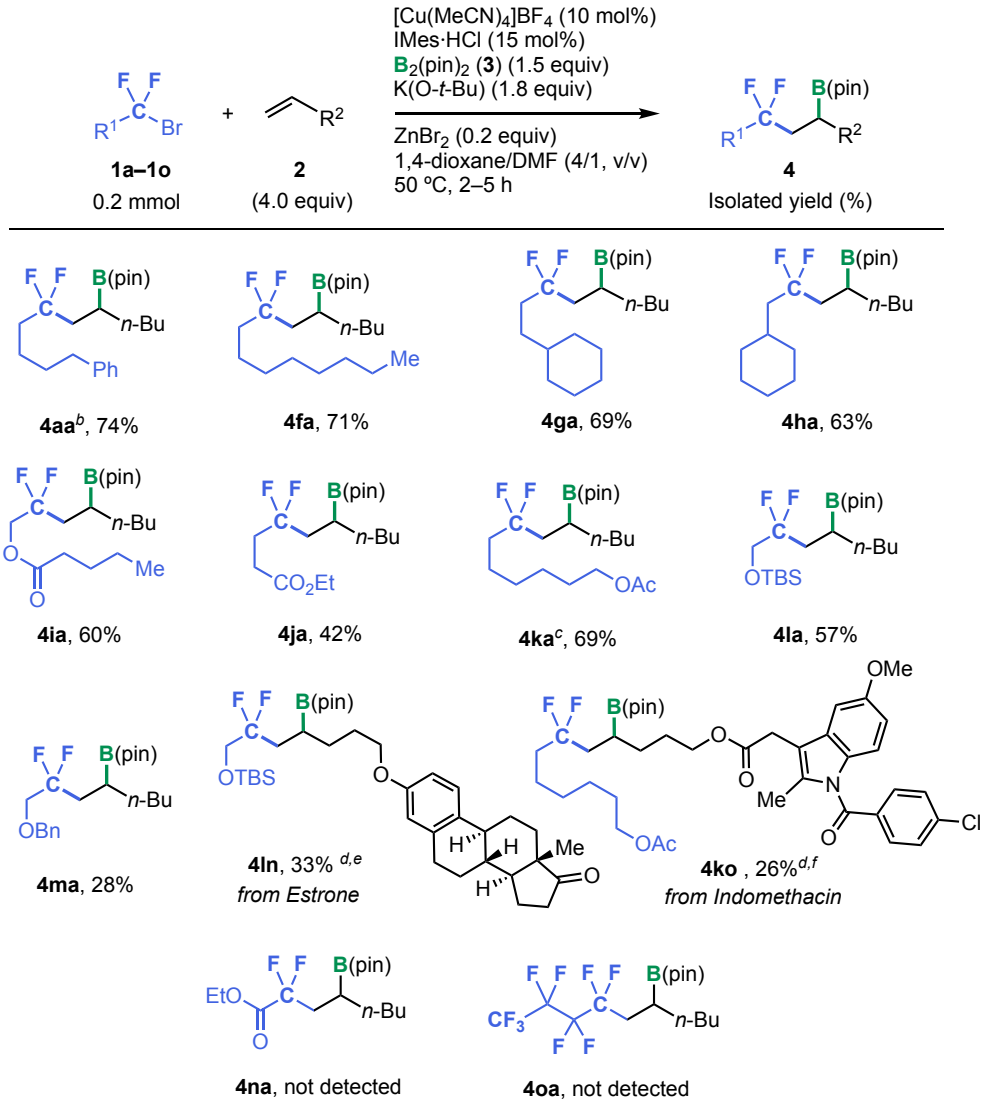



[a]Same conditions as entry 1 in Table 1 except that catalyst loadings of 10 mol% of the Cu cat. and 15 mol% of IMes·HCl were used. [b]5 mol% of Cu cat. and 7.5 mol% of IMes·HCl were used. [c]1.2 equiv. of $B_2(pin)_2$ was used. [d]The ratio of 1,4-dioxane/DMF was 6/1 (v/v). [e]d.r. was not determined. [f]Contaminated with small amounts of impurities.

Next, the author turned our attention to the scope of the α,α-difluoro alkyl bromides, which can be readily prepared from the terminal olefins in a single step (Scheme 5).[12] Using aliphatic substrates that bear *n*-hexyl or cyclohexyl groups, the corresponding products **4fa**, **4ga**, and **4ha** were obtained in good yield. Substrates that bear esters also reacted with an olefin to give

**4ia** and **4ja** in moderate yield. In addition, protecting groups such as acetyl (**4ka**), and *t*-butyl dimethyl silyl ether (**4la**) were tolerated, although a substrate bearing a benzyl ether furnished the corresponding product (**4ma**) in decreased yield. Furthermore, we conducted late-stage modifications of complex molecules such as derivatives of estrone and indomethacin, as exemplified by the efficient preparation of **4ln** and **4ko**, both of which are large molecules that bear a further transformable boron moiety. Unfortunately, γ,γ-difluoro alkyl bromo ester **1n** furnished a complex mixture under these reaction conditions. The targeted 1,2-alkylborylation product was not detected in the reaction using perfluoroalkyl iodide **1o**.

***Scheme 5.*** Scopes of difluoroalkylbromide[a]

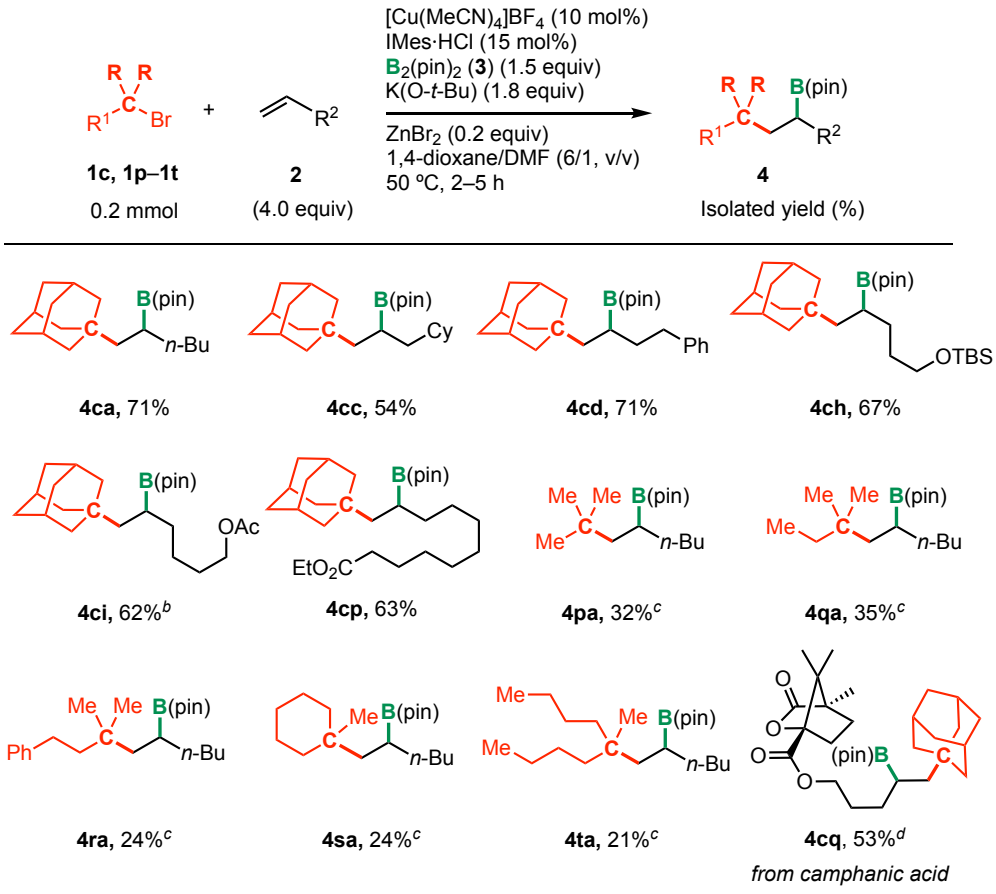



[a]Same conditions as entry 1 in Table 1 except that catalyst loadings of 10 mol% of the Cu cat. and 15 mol% of IMes·HCl were used. [b]5 mol% of Cu cat. and 7.5 mol% of IMes·HCl were used. [c]1.2 equiv. of $B_2(pin)_2$ was used. [d]The ratio of 1,4-dioxane/DMF was 6/1 (v/v). [e]d.r. was not determined.

[f]Contaminated with small amounts of impurities.

The conditions were also found to be applicable to reactions that use different tertiary alkyl bromides as the electrophile (Scheme 6). For example, the reactions between 1-adamantyl bromide (**1c**) and several different olefins afforded β-adamantyl α-alkyl boronates that bear *n*-butyl (**4ca**), cyclohexyl (**4cc**), or phenyl ethyl groups (**4cd**). Furthermore, functionalized olefins that bear a *t*-butyl dimethyl silyl ether (**2h**), an acetyl (**2i**), or an ethyl ester group (**2p**) reacted smoothly with 1-adamantyl bromide to give the corresponding products (**4ch**, **4ci**, and **4cp**) in good yield. Other tertiary alkyl bromides (**1p–1t**) also furnished the corresponding γ,γ-dialkyl α-alkyl boronates (**4pa**–**4ta**), albeit in diminished yield. Finally, I demonstrated the synthetic utility of this protocol by applying the reaction employing 1-adamantyl bromide to the late-stage modification of camphanic acid (**2q**) to provide **4cq**.

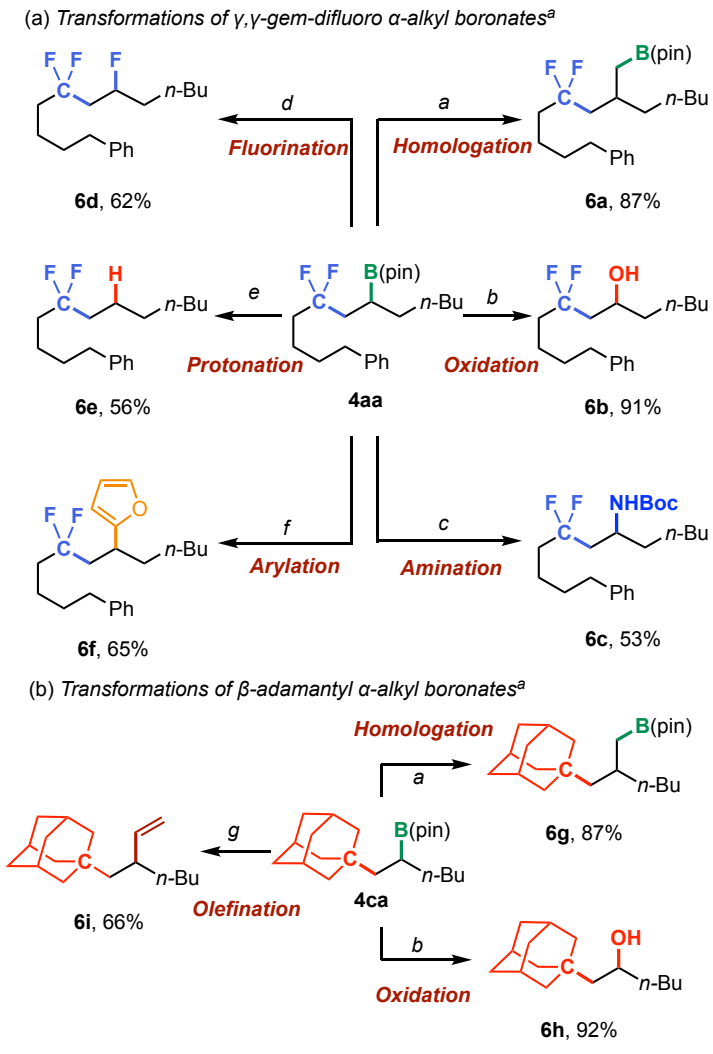
***Scheme 5.*** Scope with respect to tertiary alkyl bromides.[a]




[a]Same conditions as entry 1 in Table 1 except that catalyst loadings of 10 mol% of the Cu cat. and 15 mol% of IMes·HCl were used. [b]1.2 equiv. of $B_2(pin)_2$ was used. [c]0.4 mmol scale. The ratio of 1,4-dioxane/DMF was 4/1 (v/v). [d]d.r. was not determined.

The synthetic utility of this method was further highlighted by an array of transformations using the boron moiety (Scheme 7). First, fluorinated boronate **4aa** was subjected to a homologation with a halomethyl lithium reagent,[13] oxidation, or amination with methoxyamine[14] to give the corresponding alkylboronate (**6a**), alcohol (**6b**), or secondary amine (**6c**) in good yield (Scheme 7a). Further transformations of **4aa** undertaken include a fluorination,[15] a protonation,[16] and an oxidative coupling with furan[17] to deliver several functionalized *gem*-difluoro compounds in moderate yield (**6d-f**). Notably, the *gem*-difluoromethylene group has recently attracted attention as a valuable fluorinated motif that could be applicable in pharmaceuticals and biologically active compounds.[18,19] Additionally, β-adamantyl α-alkyl boronate **4ca** was subjected to an oxidation, a homologation, and an olefination,[20] which afforded the corresponding alkyl boronate (**6g**), alcohol (**6h**), and olefin (**6i**) in good yield (Scheme 7b).

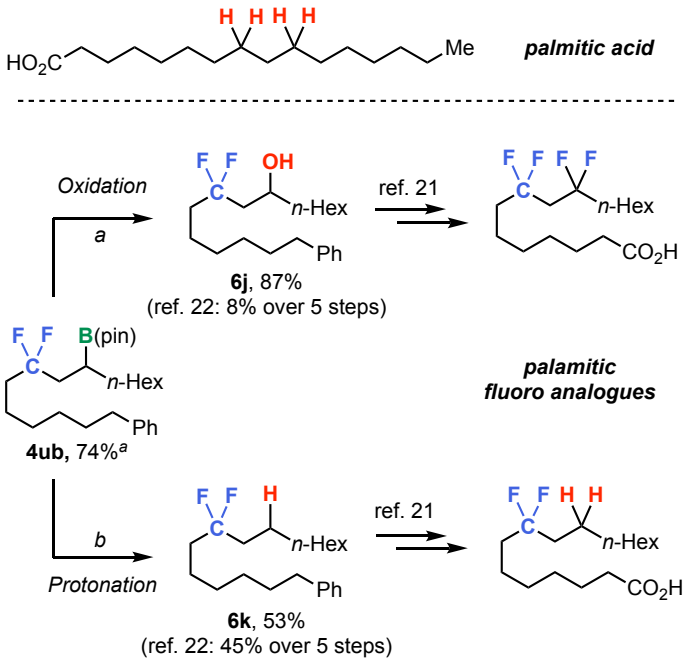
***Scheme 7.*** Several transformations of C–B bond



[a]Conditions: (a) *n*-BuLi, $BrCH_2Cl$, THF, –78 ºC to rt.; (b) 3.0 M NaOH (aq), 30% $H_2O_2$ (aq), THF, rt.; (c) *n*-BuLi, $MeONH_2$, THF, –78 ºC to 60 ºC; then $(Boc)_2O$, THF, rt.; (d) PhLi, THF, 0 ºC; then Selectfluor, MeCN, 0 ºC; (e) TBAF·$3H_2O$, $Mn(OAc)_3·2H_2O$, TBC, Toluene, 80 ºC; (f) *n*-BuLi, furan, NBS, THF, –78 ºC; (g) vinylMgBr, $I_2$, NaOMe, THF, –78 ºC to rt

The author also carried out a formal synthesis of two known *gem*-difluorinated palmitic analogues, which were synthesized by O'Hagan in multi-step syntheses for the purpose of comparing their conformational stability with that of non-fluorinated palmitic acid (Scheme 8).[21] The corresponding alcohol (**6j**) and alkyl difluorinated compound (**6k**) were synthesized in 5 steps with a total yield of 8% and 45%, respectively. In contrast, I could obtain **6j** and **6k** from the corresponding boronate **4ub** in 87% and 57% yield, respectively. As **4ub** was synthesized from commercially available 1-octene, the present procedure represents a synthetically useful and concise method for the synthesis of palmitic fluoro analogues.

***Scheme 8.*** Formal synthesis of palmitic fluoro analogues

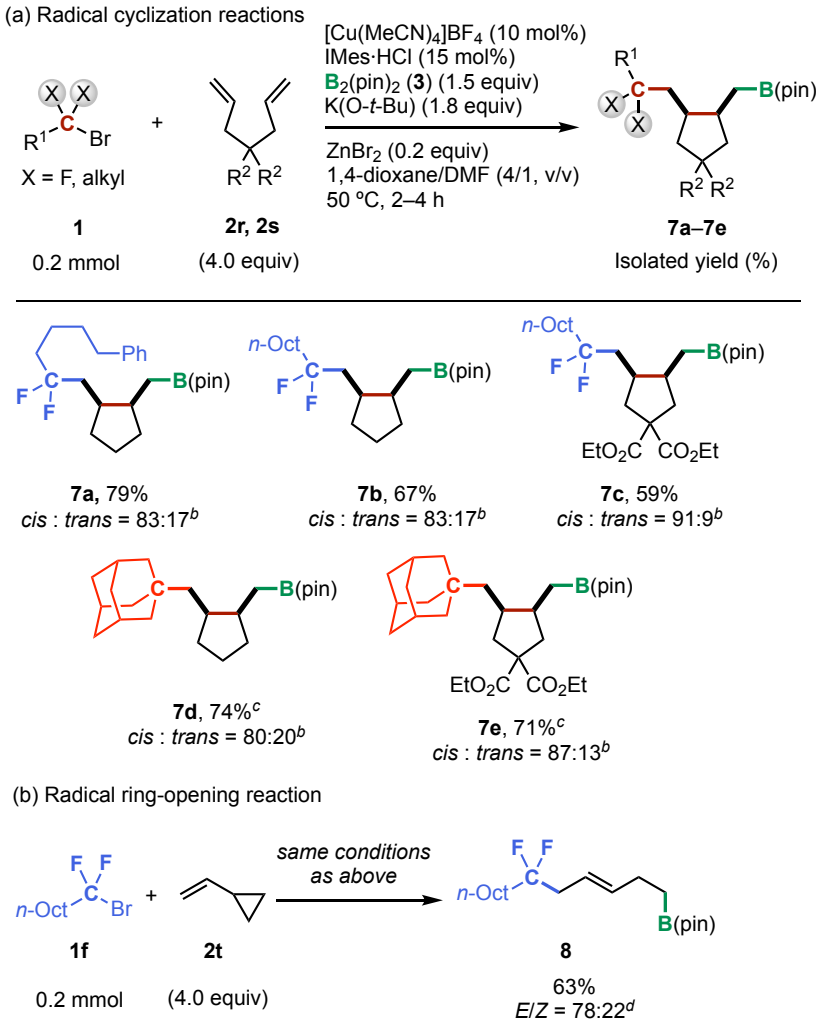



[a]Same conditions as entry 1 in Table 1 except that catalyst loadings of 10 mol% of the Cu cat. and 15 mol% of IMes·HCl were used. [b]Conditions: (a) 3.0 M NaOH (aq), 30% $H_2O_2$ (aq), THF, rt.; (b) TBAF·$3H_2O$, $Mn(OAc)_3·2H_2O$, TBC, toluene, 80 ºC.

Next, the author conducted several radical-clock experiments (Scheme 9). The reaction of α,α-difluoro alkyl bromide **1a** with 1,6-heptadiene (**2r**) gave radical-cyclized **7a** with good diastereoselectivity (Scheme 9a; 79% yield, *cis*:*trans* = 83:17), indicating a radical nature for this reaction. Other ring-closing borylated products were obtained using either diene **2r** or **2s** under the standard conditions (Scheme 9a; **7b**, **7c**) in addition to the cyclized borylated products

obtained when 1-adamantyl bromide was used (Scheme 9a; **7d**, **7e**). The radical nature of the reaction was corroborated via a radical ring-opening reaction. The reaction of α,α-difluoro alkyl bromide **1f** with vinylcyclopropane (**2t**) provided ring-opening product **8** in good yield with moderate *E*/*Z* ratio (Scheme 9b).

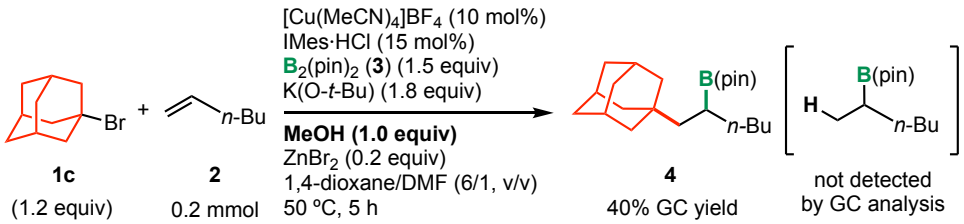
***Scheme 9.*** Radical-clock experiments




[a]Same conditions as entry 1 in Table 1 except that catalyst loadings of 10 mol% of the Cu cat. and 15 mol% of IMes·HCl were used. [b]Determined by GC analysis. [c]The ratio of 1,4-dioxane/DMF was 6/1 (v/v). [d]Determined by $^1$H NMR analysis.

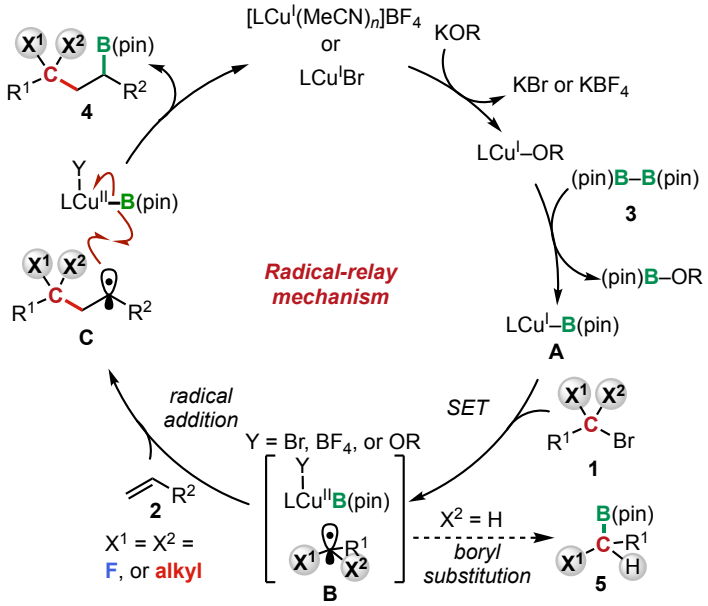
Additionally, to eliminate another possible pathway that proceeds via a two-electron mode in which a boryl copper(I) intermediate initially reacts with an olefin followed by electrophilic substitution, we conducted the 1,2-alkylborylation reaction with 1.0 equiv of MeOH as a proton source. Under the applied conditions, hydroborylation products of an olefin were not detected, which further corroborates the radical mechanism (Scheme 10).

***Scheme 10.*** The reaction with MeOH as proton source




Lastly, I would like to propose a catalytic cycle for this intermolecular 1,2-alkylborylation of olefins via a radical-relay mechanism (Scheme 11). First, the Cu(I) salt reacts with the alkoxide base to generate a copper alkoxide intermediate, which would then react with bis(pinacolato)diboron (**3**) to give boryl copper(I) intermediate **A**. Subsequent SET between intermediate **A** and alkyl halide **1** could then result in the formation of radical intermediate **B** and a boryl copper(II) intermediate.[8a,8b,9] An electronically or sterically demanding alkyl radical ($X^1$ = $X^2$ = F, or alkyl) would not undergo a boryl substitution reaction with boryl copper intermediate **A** due to the electronic effect and steric repulsion. The radical addition of an unactivated olefin provides radical intermediate **C**, although other electrophiles ($X^1$ = F or R; $X^2$ = H) prefer the boryl-substitution reaction and deliver product **5**. Finally, the radical recombination between intermediate **C** and the boryl copper(II) intermediate followed by reductive elimination releases 1,2-alkylborylation product **4** under concomitant regeneration of the copper(I) salt for the next catalytic cycle.

***Scheme 11.*** The proposed catalytic cycle



## Conclusion

As summary of this chapter, I have developed the first example of an intermolecular 1,2-alkylborylation of unactivated olefins that proceeds via a radical-relay mechanism. The key to this transformation is the use of electronically or sterically demanding alkyl electrophiles, which suppress the competing direct boryl substitution reactions, thus allowing the intermolecular alkylborylation product to be obtained with excellent selectivity. The synthetic utility of this protocol was demonstrated by versatile transformations of the resulting boryl groups to furnish valuable functionalized molecules.

# Experiment

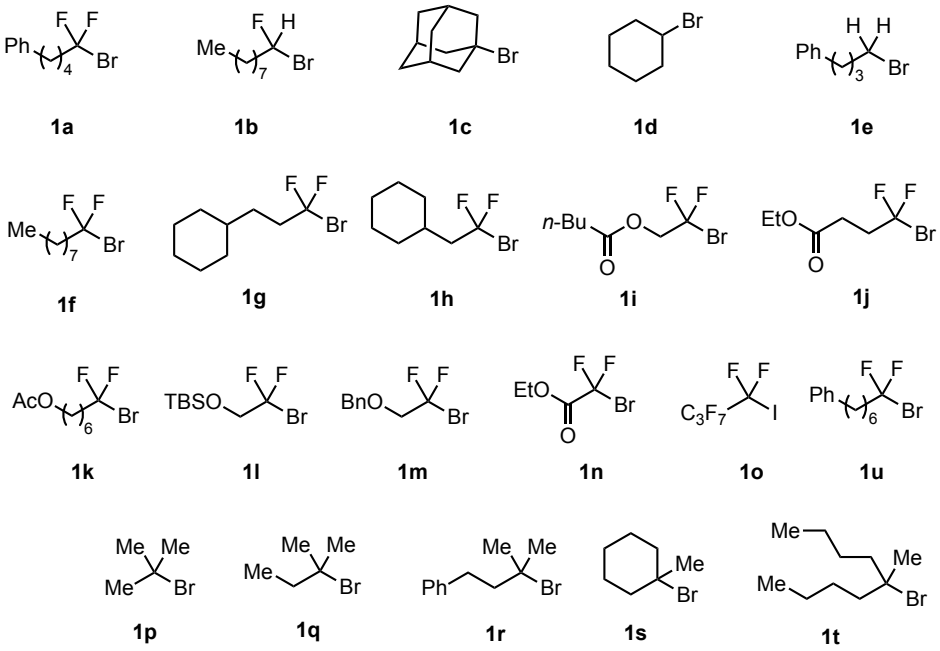
## General

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 ($^{1}$H: 400 MHz, $^{13}$C: 100 MHz, and $^{19}$F: 373 MHz). Tetramethylsilane ($^{1}$H), $CDCl_3$ ($^{1}$H, $^{13}$C), and fluorobenzene ($^{19}$F, δ –113.60) were employed as the external standards. Multiplicity was recorded as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. 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 an 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 Global Facility Center, Hokkaido University. The reactions with Blue LED were carried out by using Kessil A 150WE TUNA Blue. Single crystal X-ray structural analysis was carried out on a Rigaku XtaLAB PRO MM007 diffractometer using graphite monochromated Cu-Kα 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 Olex2 crystallographic software package except for refinement, which was performed using SHELXL-2013.

## Substrate Preparation Procedures

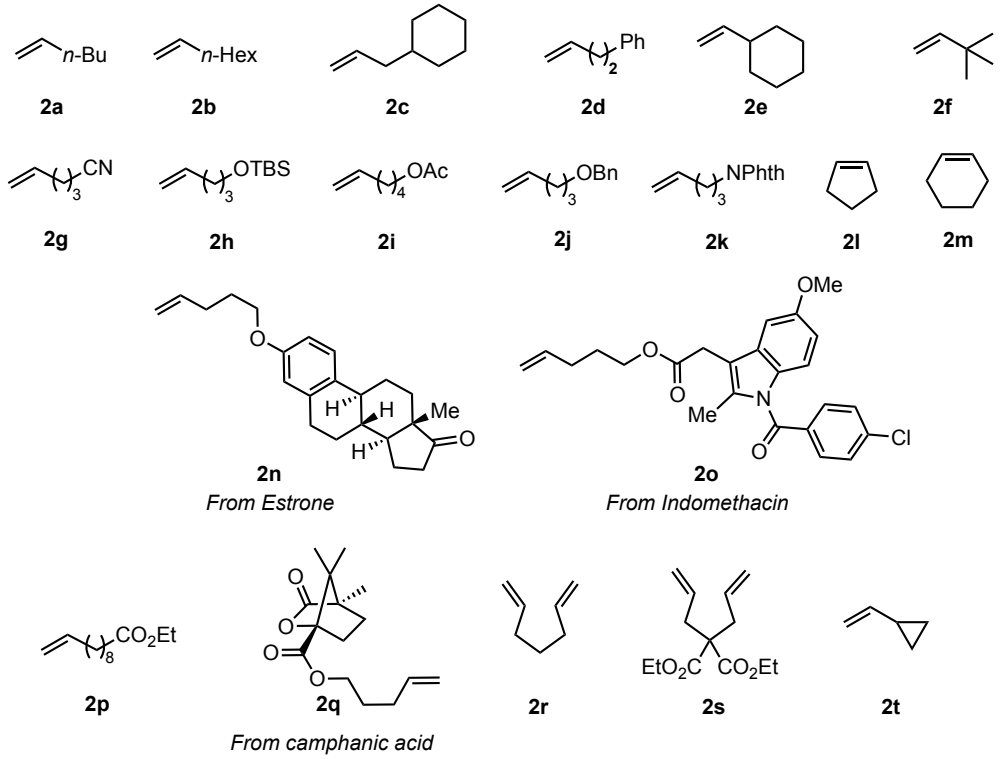
The fluorinated alkyl bromides **1a**[12], **1b**[22], **1f**[23], **1g**[12], **1i**[24], **1j**[23], **1l**[25], and **1m**[26] are known compounds and were prepared in accordance to references. The new compounds **1h**, **1k** and **1u** were synthesized according to references and characterized described below. The tertiary alkyl bromides **1c–1e**, **1p**–**1q** were purchased from commercial suppliers. Tertiary alkyl bromides **1r**[27], **1s**[27], and **1t**[28] are known compounds and were prepared in accordance to references. All spectroscopic data were matched in those reported.

**Table S1. Alkyl bromide used in this study**



The olefins **2a**–**2g**, **2i**, **2l**, **2m**, **2p**, **2r**–**2t** were purchased from commercial suppliers. The functionalized olefins (**2h**[29], **2j**[30], **2k**[31], **2n**[32], **2o**[33], and **2q**[34]) are known compounds and were prepared in accordance to references. All spectroscopic data were matched in those reported.

**Table S2. Olefins used in this study**




**2a** **2b** **2c** **2d** **2e** **2f**

**2g** **2h** **2i** **2j** **2k** **2l** **2m**

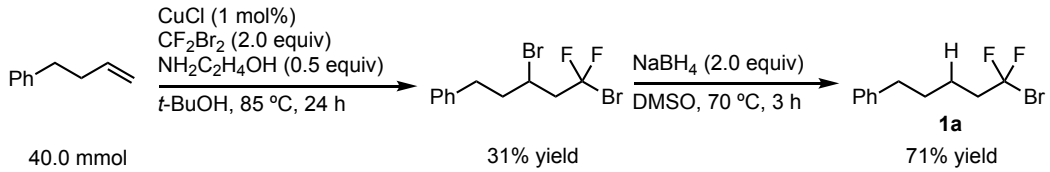
**2n**
*From Estrone*

**2o**
*From Indomethacin*

**2p** **2q** **2r** **2s** **2t**

*From camphanic acid*

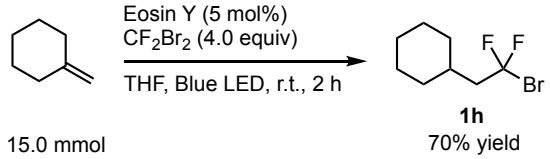
**Preparation of (5-bromo-5,5-difluoropentyl)benzene (1a).[24]**




A CuCl (40.0 mg, 0.4 mmol), 1-aminoethanol (1.2 mL, 20.0 mmol) and 4-phenyl-1-butene (1.0 g, 40.0 mmol) were dissolved in anhydrous *t*-BuOH (6.6 mL), then the $CF_2Br_2$ (7.4 mL, 60.0 mmol) was added to the reaction mixture in one portion at 0 ºC under a nitrogen atmosphere. The mixture was allowed to warm up to 85 ºC and stir for 24 h. After that, the reaction mixture was passed through a silica gel short column to remove the Cu catalyst, and the volatiles were removed in vacuo. The brown oil residue was purified by Kugelrohr distillation under a reduced pressure ($6.0\times10^{-1}$ hPa, 120 ºC) to give target difluoro alkyl bromide (4.3 g, 31% yield) as a colorless oil.

The resultant product (4.3 g, 12.6 mmol) was dissolved in DMSO (17.5 mL) and then $NaBH_4$ was added to this reaction mixture (951 mg, 25.2 mmol) in several portions under a nitrogen atmosphere. The mixture was allowed to stir at 70 ºC for 3 h. After that, the mixture was diluted with $Et_2O$ at 0 ºC, quenched by 3M $HCl_{aq}$, and the mixture was extracted with $Et_2O$ three times. The combined organic layer was washed with water three times. Then the organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The brown oil residue was purified by Kugelrohr distillation under a reduced pressure ($6.0\times10^{-1}$ hPa, 100 ºC) to give **1a** (2.4 g, 71% yield) as a colorless oil. The spectroscopic data was matched with the literature.[24]

**Preparation of (2-bromo-2,2-difluoroethyl)cyclohexane (1h).[12]**

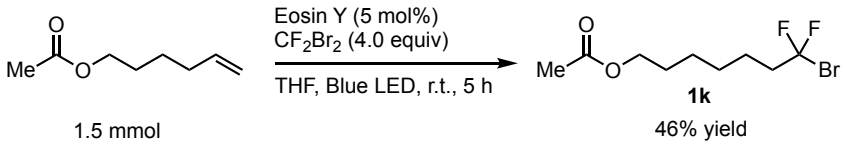



A 100 mL two-necked flask was charged with Eosin Y (48.6 mg, 0.075 mmol) and the olefin (180.3 μL, 1.5 mmol) in THF (45 mL). Then $CF_2Br_2$ (554 μL, 6.0 mmol) was added in one portion at 0 ºC to the reaction mixture before the mixture was degassed three times by the freeze–pump–thaw procedure. The flask was placed at a distance of 2 cm from the blue LEDs, and the mixture was stirred under a nitrogen atmosphere with irradiation by blue LEDs for 2 h. After the volatiles were removed in vacuo, the oily residue was subjected to silica gel chromatography (pentane) to give **1h** (237 mg, 70% yield) as a colorless oil.

$^1$H NMR (399 MHz, $CDCl_3$): δ 0.96–1.36 (m, 5H), 1.61–1.87 (m, 6H), 2.28 (td, $J$ = 6.0, 15.6 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 25.9 (*C*H), 33.1 (*C*H), 34.2 (*C*H), 51.3 (t, $J$ = 19.9 Hz, *C*$H_2$), 123.1 (t, $J$ = 308.3 Hz, *C*$F_2$). $^{19}$F NMR (373 MHz, $CDCl_3$): δ –41.0 (t, $J$ = 15.3 Hz, 2F). HRMS–FI

(*m*/*z*): $[M]^+$ calcd for $C_8H_{13}BrF_2$, 226.0169; found, 226.0177.

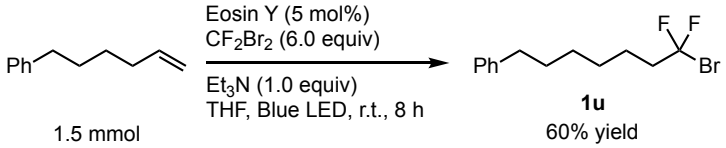
**Preparation of 5-bromo-5,5-difluoropentyl acetate (1k).[12]**




**1k** was prepared from the corresponding olefin (214.4 mg, 1.5 mmol) under the blue LED conditions according to the procedure described above. The product **1k** was obtained in 47% yield (191.2 mg).

$^1$H NMR (392 MHz, $CDCl_3$): δ 1.32–1.47 (m, 4H), 1.59–1.72 (m, 4H), 2.05 (s, 3H), 2.27–2.43 (m, 2H), 4.06 (t, $J$ = 6.5 Hz, 2H). $^{13}$C NMR (99 MHz, $CDCl_3$): δ 20.9 (*C*$H_3$), 23.8 (*C*$H_2$), 25.6 (*C*$H_2$), 28.0 (*C*$H_2$), 28.3 (*C*$H_2$), 44.1 (t, $J$ = 21.3 Hz, *C*H), 64.2 (*C*$H_2$), 123.0 (t, $J$ = 306.9 Hz, *C*$F_2$), 171.1 (*C*). $^{19}$F NMR (373 MHz, $CDCl_3$): δ –44.1 to –43.9 (m, 2F). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_9H_{15}O_2BrF_2Na$, 295.0121; found, 295.0109.

**Preparation of (7-bromo-7,7-difluoroheptyl)benzene (1u).[12]**




A 100 mL two-necked flask was charged with Eosin Y (48.6 mg, 0.075 mmol), $Et_3N$ (209.1 μL, 1.5 mmol), and the olefin (251.6 mg, 1.6 mmol) in THF (45 mL). Then $CF_2Br_2$ (554 μL, 6.0 mmol) was added in one portion at 0 ºC to the reaction mixture before the mixture was degassed three times by the freeze–pump–thaw procedure. The flask was placed at a distance of 2 cm from the blue LEDs and the mixture was stirred under a nitrogen atmosphere and irradiated by blue LEDs for 3 h. After that, the second portion of $CF_2Br_2$ (250 μL, 3.0 mmol) was added to the reaction mixture. Then the mixture was stirred for another 5 h. The volatiles were removed in vacuo, and the oily residue was subjected to silica gel chromatography (hexane) to give **1u** (260.8 mg, 57% yield) as a colorless oil.

$^1$H NMR (396 MHz, $CDCl_3$): δ 1.32–1.45 (m, 4H), 1.58–1.68 (m, 4H), 2.26–2.39 (m, 2H), 2.61 (t, $J$ = 7.7 Hz, 2H), 7.15–7.21 (m, 3H), 7.25–7.31 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 23.8 (*C*$H_2$), 28.3 (*C*$H_2$), 28.8 (*C*$H_2$), 31.2 (*C*$H_2$), 35.8 (*C*$H_2$), 44.2 (t, $J$ = 21.1 Hz, *C*$H_2$), 123.2 (t, $J$ = 307.1 Hz, *C*$F_2$), 125.7 (*C*H), 128.3 (*C*H), 128.4 (*C*H), 142.5 (*C*). $^{19}$F NMR (373 MHz, $CDCl_3$): δ –43.9 to –43.7 (m, 2F). HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{13}H_{17}BrF_2$, 290.0482; found, 290.0479.

## General Borylation Procedures

**Procedure of the copper(I)-catalyzed 1,2-alkyl borylation for 4aa (Condition A).**

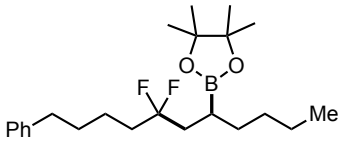
An oven-dried reaction vial was charged with bis(pinacolato)diboron (**3**) (38.1 mg, 0.15 mmol), IMes•HCl (2.5 mg, 0.0075 mmol) and transferred to an argon-filled glove box. $[Cu(MeCN)_4]BF_4$ (1.5 mg, 0.005 mmol), $ZnBr_2$ (4.5 mg, 0.02 mmol), and K(O-*t*-Bu) (20.2 mg, 0.18 mmol) were placed in the reaction vial, and then the vial was capped with a rubber septum and removed from the glovebox. The vial with reagents was refiled with a nitrogen atmosphere and the solids were suspended in 1,4-dioxane/DMF (200 μL/50 μL), then the suspension was allowed to stir for 1 min at r.t. After that, olefin **2a** (100.8 μL, 0.80 mmol) and alkyl electrophile **1a** (26.3 mg, 0.10 mmol) were subsequently added to the suspension at r.t., then the mixture was allowed to stir at 50 ºC. After completing the reaction, the mixture was passed through a short plug of silica gel (Φ: 10 mm, the height of the silica-gel column: 30 mm), eluted with $Et_2O$, and the volatiles were removed in vacuo. The resulting oily residue was subjected to silica gel chromatography ($Et_2O$/hexane, typically 0:100–4:96) to give the corresponding borylation product **4aa** as a colorless oil.

**Procedure of the copper(I)-catalyzed 1,2-alkyl borylation for 4ca (Condition B).**

An oven-dried reaction vial was charged with bis(pinacolato)diboron (**3**) (76.2 mg, 0.3 mmol), IMes•HCl (10.2 mg, 0.03 mmol) and transferred to an argon-filled glove box. $[Cu(MeCN)_4]BF_4$ (6.3 mg, 0.02 mmol), $ZnBr_2$ (9.0 mg, 0.04 mmol), and K(O-*t*-Bu) (40.4 mg, 0.36 mmol) were placed in the reaction vial, then the vial was capped with a rubber septum and removed from the glovebox. The vial with reagents was refiled with a nitrogen atmosphere and the solids were suspended in 1,4-dioxane/DMF (300 μL/100 μL), then the suspension was allowed to stir for 1 min at r.t. After that, olefin **2a** (100.5 μL, 0.80 mmol) and alkyl electrophile **1c** (43.1 mg, 0.20 mmol) in 1,4-dioxane (300 μL) were subsequently added to the suspension at r.t., then the mixture was allowed to stir at 50 ºC. After completing the reaction, the mixture was passed through a short plug of silica gel (Φ: 10 mm, the height of the silica-gel column: 30 mm), eluted with $Et_2O$, and volatiles were removed in vacuo. The resulting oily residue was subjected to silica gel chromatography ($Et_2O$/hexane, typically 0:100–4:96) to give the corresponding borylation product **4ca** as a colorless oil.

## Borylation Product Characterizations

**2-(7,7-Difluoro-11-phenylundecan-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4aa).**

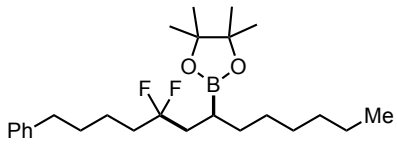



**4aa**

Prepared according to condition **A** described above. The reaction was conducted for 2 h with 53.6 mg (0.20 mmol) of **1a** and 100.8 μL (0.80 mmol) of **2a**. The product **4aa** was obtained in 73% yield (58.5 mg).

$^{1}$H NMR (392 MHz, $CDCl_3$): δ 0.88 (t, $J$ = 6.9 Hz, 3H), 1.13–1.37 (m, 7H), 1.24 (s, 12H), 1.39–1.54 (m, 3H), 1.60–1.69 (m, 2H), 1.75–1.91 (m, 2H), 1.93–2.10 (m, 1H), 2.62 (t, $J$ = 7.6 Hz, 2H), 7.14–7.21 (m, 3H), 7.24–7.31 (m, 2H). $^{13}$C NMR (99 MHz, $CDCl_3$): δ 14.0 ($C$H$_3$), 17.3 (br, B–$C$H), 22.0 (t, $J$ = 4.7 Hz, $C$H$_2$), 22.8 ($C$H$_2$), 24.70 ($C$H$_3$), 24.74 ($C$H$_3$), 31.1 ($C$H$_2$), 31.2 ($C$H$_2$), 31.4 ($C$H$_2$), 35.7 ($C$H$_2$) 36.5 (t, $J$ = 25.5 Hz, $C$H$_2$), 38.4 (t, $J$ = 25.1 Hz, $C$H$_2$), 83.1 ($C$), 125.4 (t, $J$ = 241.7 Hz, $C$F$_2$), 125.7 ($C$H), 128.27 ($C$H), 128.33 ($C$H), 142.2 ($C$). $^{19}$F NMR (369 MHz, $CDCl_3$): δ –97.8 to –95.6 (m, 2F). HRMS–ESI ($m/z$): $[M+Na]^+$ calcd for $C_{23}H_{37}{}^{11}BF_2O_2Na$, 417.2751; found, 417.2747.

**2-(5,5-Difluoro-1-phenyltridecan-7-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4ab).**

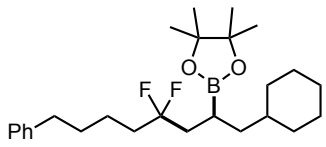



**4ab**

Prepared according to condition **A** described above, except the catalyst loading {10 mol% of $[Cu(MeCN)_4]BF_4$ and 15 mol% of IMes•HCl were used.}. The reaction was conducted for 2 h with 52.6 mg (0.20 mmol) of **1a** and 125.2 μL (0.80 mmol) of **2b**. The product **4ab** was obtained in 66% yield (55.6 mg).

$^{1}$H NMR (392 MHz, $CDCl_3$): δ 0.87 (t, $J$ = 6.9 Hz, 3H), 1.13–1.37 (m, 11H), 1.23 (s, 12H), 1.37–1.55 (m, 3H), 1.60–1.69 (m, 2H), 1.74–1.91 (m, 2H), 1.93–2.09 (m, 1H), 2.62 (t, $J$ = 7.6 Hz, 2H), 7.14–7.21 (m, 3H), 7.24–7.31 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 14.1 ($C$H$_3$), 17.3 (br, B–$C$H), 22.1 (t, $J$ = 4.3 Hz, $C$H$_2$), 22.6 ($C$H$_2$), 24.72 ($C$H$_3$), 24.75 ($C$H$_3$), 28.8 ($C$H$_2$), 29.4 ($C$H$_2$), 31.2 ($C$H$_2$), 31.7 ($C$H$_2$), 31.8 ($C$H$_2$), 35.7 ($C$H$_2$), 36.5 (t, $J$ = 25.1 Hz, $C$H$_2$), 38.4 (t, $J$ = 25.1 Hz, $C$H$_2$), 125.4 (t, $J$ = 239.0 Hz, $C$F$_2$), 125.7 ($C$H), 128.28 ($C$H), 128.34 ($C$H), 142.2 ($C$). $^{19}$F NMR (373 MHz, $CDCl_3$): δ –97.8 to –95.6 (m, 2F). HRMS–ESI ($m/z$): $[M+Na]^+$ calcd for $C_{25}H_{41}O_2{}^{11}BF_2Na$, 445.3064; found, 445.3053.

**2-(1-Cyclohexyl-4,4-difluoro-8-phenyloctan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4ac).**

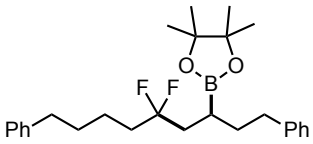



**4ac**

Prepared according to condition **A** described above. The reaction was conducted for 2 h with 52.6 mg (0.20 mmol) of **1a** and 123.8 μL (0.80 mmol) of **2c**. The product **4ac** was obtained in 65% yield (56.6mg).

$^{1}$H NMR (401 MHz, $CDCl_3$): δ 0.84 (q, *J* = 6.7 Hz, 2H), 1.11–1.21 (m, 4H), 1.23 (s, 12H), 1.28–1.37 (m, 2H), 1.45–1.55 (m, 2H), 1.60–1.72 (m, 7H), 1.73–2.06 (m, 5H), 2.62 (t, *J* = 7.6 Hz, 2H), 7.14–7.21 (m, 3H), 7.25–7.30 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 14.3 (br, B–*C*H), 22.1 (*C*$H_2$), 24.7 (*C*$H_3$), 24.8 (*C*$H_3$), 26.3 (*C*$H_2$), 26.4 (*C*$H_2$), 26.6 (*C*$H_2$), 31.2 (*C*$H_2$), 33.1 (*C*$H_2$), 33.6 (*C*$H_2$), 35.7 (*C*$H_2$), 36.5 (t, *J* = 25.4 Hz, *C*$H_2$), 36.7 (*C*H), 38.7 (t, *J* = 25.4 Hz, *C*$H_2$), 39.4 (*C*$H_2$), 83.0 (*C*), 125.4 (t, *J* = 241.9 Hz, *C*$F_2$), 125.7 (*C*H), 128.28 (*C*H), 128.34 (*C*H), 142.2 (*C*). $^{19}$F NMR (369 MHz, $CDCl_3$): δ –97.7 to –95.3 (m, 2F). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{26}H_{41}O_2{}^{11}BF_2Na$, 457.3065; found, 457.3054.

**7,7-Difluoro-11-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)undecanenitrile (4ad).**

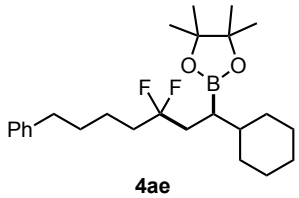



**4ad**

Prepared according to condition **A** described above, except the catalyst loading {10 mol% of $[Cu(MeCN)_4]BF_4$ and 15 mol% of IMes•HCl were used.}. The reaction was conducted for 3 h with 52.6 mg (0.20 mmol) of **1a** and 120.1 μL (0.80 mmol) of **2d**. The product **4ad** was obtained in 58% yield (50.9 mg).

$^{1}$H NMR (392 MHz, $CDCl_3$): δ 1.26 (s, 12H), 1.45–1.55 (m, 2H), 1.58–1.71 (m, 4H), 1.72–1.94 (m, 4H), 1.98–2.15 (m, 1H), 2.61 (t, *J* = 7.8 Hz, 4H), 7.13–7.21 (m, 6H), 7.23–7.31 (m, 4H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 17.3 (br, B–*C*H), 22.0 (t, *J* = 4.3 Hz, *C*$H_2$), 24.8 (*C*$H_3$), 31.2 (*C*H), 33.8 (*C*H), 35.3 (*C*H), 35.7 (*C*H), 36.6 (t, *J* = 25.4 Hz, *C*$H_2$), 38.1 (t, *J* = 24.9 Hz, *C*$H_2$), 83.2 (*C*), 125.4 (t, *J* = 241.9 Hz, *C*$F_2$), 125.7 (*C*H), 128.29 (*C*H), 128.34 (*C*H), 142.2 (*C*), 142.4 (*C*). $^{19}$F NMR (373 MHz, $CDCl_3$): δ –97.7 to –95.5 (m, 2F). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{27}H_{37}O_2{}^{11}BF_2Na$, 465.2752; found, 465.2741.

**2-(1-Cyclohexyl-3,3-difluoro-7-phenylheptyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4ae).**

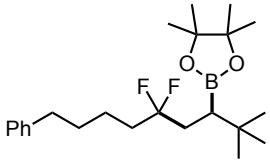



**4ae**

Prepared according to condition **A** described above, except the catalyst loading {10 mol% of $[Cu(MeCN)_4]BF_4$ and 15 mol% of IMes•HCl were used.}. The reaction was conducted for 3 h with 52.1 mg (0.20 mmol) of **1a** and 109.5 μL (0.80 mmol) of **2e**. The product **4ae** was obtained in 64% yield (54.0 mg).

$^1$H NMR (392 MHz, $CDCl_3$): δ 0.91–1.28 (m, 6H), 1.24 (s, 12H), 1.29–1.41 (m, 1H), 1.45–1.55 (m, 2H), 1.60–1.92 (m, 10H), 2.00–2.14 (m, 1H), 2.62 (t, $J$ = 7.6 Hz, 2H), 7.14–7.21 (m, 3H), 7.24–7.32 (m, 2H). $^{13}$C NMR (99 MHz, $CDCl_3$): δ 22.0 (t, $J$ = 4.1 Hz, $CH_2$), 23.8 (br, B–$CH$), 24.8 ($CH_3$), 24.9 ($CH_3$), 26.6 (t, $J$ = 5.6 Hz, $CH_2$), 31.2 ($CH_2$), 32.0 ($CH_2$), 32.6 ($CH_2$), 35.7 ($CH_2$), 35.9 (t, $J$ = 24.6 Hz, $CH_2$), 36.5 (t, $J$ = 26.0 Hz, $CH_2$), 40.0 ($CH$), 83.1 ($C$), 125.68 (t, $J$ = 241.7 Hz, $CF_2$), 125.69 ($CH$), 128.26 ($CH$), 128.33 ($CH$), 142.2 ($C$). $^{19}$F NMR (373 MHz, $CDCl_3$): δ –98.8 to –95.6 (m, 2F). HRMS–ESI ($m/z$): $[M+Na]^+$ calcd for $C_{25}H_{39}O_2{}^{11}BF_2Na$, 443.2908; found, 443.2900.

**2-(5,5-Difluoro-2,2-dimethyl-9-phenylnonan-3-yl)-4,4,5,5-tetramethyl-1,3,2 dioxaborolane (4af).**

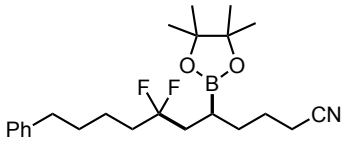



**4af**

Prepared according to condition **A** described above, except the catalyst loading {10 mol% of $[Cu(MeCN)_4]BF_4$ and 15 mol% of IMes•HCl were used.}. The reaction was conducted for 2 h with 52.6 mg (0.20 mmol) of **1a** and 103.6 μL (0.80 mmol) of **2f**. The product **4af** was obtained in 49% yield (38.9 mg) with small amounts of unidentified byproducts.

$^1$H NMR (396 MHz, $CDCl_3$,): δ 0.94 (s, 9H), 1.24 (s, 12H), 1.48–1.55 (m, 2H), 1.60–1.92 (m, 6H), 1.96–2.14 (m, 1H), 2.62 (t, $J$ = 7.7 Hz, 2H), 7.14–7.22 (m, 3H), 7.24–7.32 (m, 2H). $^{13}$C NMR (99 MHz, $CDCl_3$): δ 22.0 (t, $J$ = 4.8 Hz, $CH_2$), 24.8 ($CH_3$), 25.0 ($CH_3$), 29.2 ($CH_3$), 31.2 ($CH_2$), 31.7 ($C$), 34.2 (t, $J$ = 24.6 Hz, $CH_2$), 35.7 ($CH_2$), 36.5 (t, $J$ = 25.5 Hz, $CH_2$), 83.1 ($C$), 125.72 ($CH$), 125.76 (t, $J$ = 235.1 Hz, $CF_2$), 128.28 ($CH$), 128.34 ($CH$), 142.2 ($C$). The carbon directly attached to the boron atom was not detected. $^{19}$F NMR (373 MHz, $CDCl_3$): δ –97.9 to –95.1 (m, 2F). HRMS–ESI ($m/z$): $[M+Na]^+$ calcd for $C_{23}H_{37}O_2{}^{11}BF_2Na$, 417.2751; found, 417.2742.

**7,7-Difluoro-11-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)undecanenitrile (4ag).**

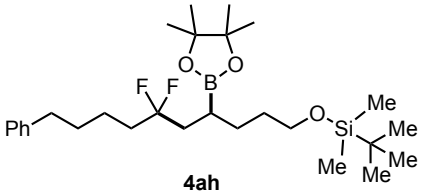



**4ag**

Prepared according to condition **A** described above. The reaction was conducted for 3 h with 53.2 mg (0.20 mmol) of **1a** and 90.9 μL (0.80 mmol) of **2g**. The product **4ag** was obtained in 52% yield (42.9 mg).

$^{1}$H NMR (401 MHz, $CDCl_3$): δ 1.19–1.29 (m, 2H), 1.23 (s, 12H), 1.47–1.54 (m, 2H), 1.60–1.71 (m, 5H), 1.75–1.91 (m, 3H), 1.96–2.14 (m, 1H), 2.34 (t, *J* = 7.0 Hz, 2H), 2.62 (t, *J* = 7.6 Hz, 2H), 7.14–7.21 (m, 3H), 7.24–7.31 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 16.5 (br, B–*C*H), 17.2 (*C*$H_2$), 22.1 (t, *J* = 4.3 Hz, *C*$H_2$), 24.7 (*C*$H_3$), 24.7 (*C*$H_2$), 30.6 (*C*$H_2$), 31.1 (*C*$H_2$), 35.7 (*C*$H_2$), 36.8 (t, *J* = 25.9 Hz, *C*$H_2$), 38.0 (t, *J* = 25.4 Hz, *C*$H_2$), 83.4 (*C*), 119.5 (*C*), 125.3 (t, *J* = 242.4 Hz, *C*$F_2$), 125.7 (*C*H), 128.28 (*C*H), 128.33 (*C*H), 142.1 (*C*). $^{19}$F NMR (369 MHz, $CDCl_3$): δ –98.2 to –96.1 (m, 2F). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{23}H_{34}O_2N^{11}BF_2Na$, 428.2547; found, 428.2538.

***tert*-Butyl[(6,6-difluoro-10-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)decyl)oxy]dimethylsilane (4ah).**



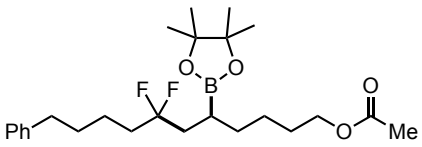

**4ah**

Prepared according to procedure **A** described above, except the catalyst loading {10 mol% of $[Cu(MeCN)_4]BF_4$ and 15 mol% of IMes•HCl was used.}. The reaction was conducted for 2 h with 52.8 mg (0.20 mmol) of **1a** and 197.0 μL (0.80 mmol) of **2h**. The product **4ah** was obtained in 61% yield (62.6 mg).

$^{1}$H NMR (401 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.88 (s, 9H), 1.14–1.29 (m, 2H), 1.23 (s, 12H), 1.31–1.55 (m, 6H), 1.58–1.71 (m, 2H), 1.72–1.92 (m, 2H), 1.93–2.15 (m, 1H), 2.62 (t, *J* = 7.6 Hz, 2H), 3.59 (t, *J* = 6.4 Hz, 2H), 7.14–7.21 (m, 3H), 7.23–7.31 (m, 2H).$^{13}$C NMR (99 MHz, $CDCl_3$): δ –5.3 (*C*$H_3$), 17.0 (br, B–*C*H), 18.3 (*C*), 22.1 (t, *J* = 4.3 Hz, *C*$H_2$), 24.7 (*C*$H_3$), 26.0 (*C*$H_3$), 27.9 (*C*$H_2$), 31.2 (*C*$H_2$), 32.1 (*C*$H_2$), 35.7 (*C*$H_2$), 36.6 (t, *J* = 26.0 Hz, *C*$H_2$), 38.4 (t, *J* = 25.0 Hz, *C*$H_2$), 63.2 (*C*$H_2$), 83.1 (*C*), 125.4 (t, *J* = 241.7 Hz, *C*$F_2$), 125.7 (*C*H), 128.3 (*C*H), 128.4 (*C*H), 142.2 (*C*). $^{19}$F NMR (373 MHz, $CDCl_3$): δ –98.2 to –95.4 (m, 2F). HRMS-ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{28}H_{49}{}^{11}BF_2O_3SiNa$,

533.3410; found, 533.3404.

**7,7-Difluoro-11-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)undecyl acetate (4ai).**

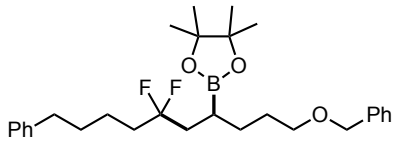



**4ai**

Prepared according to procedure **A** described above, except the catalyst loading {10 mol% of $[Cu(MeCN)_4]BF_4$ and 15 mol% of IMes•HCl was used.} with 1.2 equiv of $B_2(pin)_2$. The reaction was conducted for 2 h with 52.8 mg (0.20 mmol) of **1a** and 130.0 μL (0.82 mmol) of **2i**. The product **4ai** was obtained in 55% yield (49.5 mg).

$^1$H NMR (401 MHz, $CDCl_3$): δ 1.18–1.28 (m, 2H), 1.23 (s, 12H), 1.33–1.42 (m, 2H), 1.45–1.55 (m, 2H), 1.58–1.69 (m, 5H), 1.75–1.91 (m, 3H), 1.94–2.11 (m, 1H), 2.03 (s, 3H), 2.62 (t, $J$ = 7.4 Hz, 2H), 4.04 (t, $J$ = 6.6 Hz, 2H), 7.14–7.21 (m, 3H), 7.24–7.30 (m, 2H). $^{13}$C NMR (99 MHz, $CDCl_3$): δ 17.3 (br, B–*C*H), 20.9 (*C*H$_3$), 22.0 (t, $J$ = 4.3 Hz, *C*H$_2$), 24.69 (*C*H$_3$), 24.72 (*C*H$_3$), 25.2 (*C*H$_2$), 28.6 (*C*H$_2$), 31.2 (*C*H$_2$), 31.3 (*C*H$_2$), 35.7 (*C*H$_2$), 36.6 (t, $J$ = 25.5 Hz, *C*H$_2$), 38.2 (t, $J$ = 25.0 Hz, *C*H$_2$), 64.4 (*C*H$_2$), 83.2 (*C*), 125.3 (t, $J$ = 241.7 Hz, *C*F$_2$), 125.7 (*C*H), 128.26 (*C*H), 128.32 (*C*H), 142.2 (*C*), 171.1 (*C*). $^{19}$F NMR (373 MHz, $CDCl_3$): δ –98.0 to –95.5 (m, 2F). HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{25}H_{39}{}^{11}BF_2O_4Na$, 475.2806; found, 475.2803.

**2-[1-(Benzyloxy)-6,6-difluoro-10-phenyldecan-4-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4aj).**



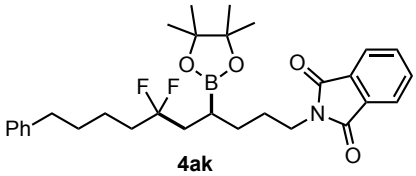

**4aj**

Prepared according to procedure **A** described above, except the catalyst loading {10 mol% of $[Cu(MeCN)_4]BF_4$ and 15 mol% of IMes•HCl was used.}. The reaction was conducted for 3 h with 53.1 mg (0.20 mmol) of **1a** and 150.0 μL (0.80 mmol) of **2b**. The product **4aj** was obtained in 30% yield (29.2 mg).

$^1$H NMR (401 MHz, $CDCl_3$): δ 1.23 (s, 12H), 1.37–1.57 (m, 4H), 1.59–1.68 (m, 5H), 1.73–1.91 (m, 3H), 1.94–2.11 (m, 1H), 2.61 (t, $J$ = 7.8 Hz, 2H), 3.46 (t, $J$ = 6.4 Hz, 2H), 4.49 (s, 2H), 7.14–7.20

(m, 3H), 7.24–7.27 (m, 3H), 7.30–7.35 (m, 4H). $^{13}$C NMR (99 MHz, $CDCl_3$): δ 17.1 (br, B–*C*H), 22.0 (t, *J* = 4.2 Hz ,*C*$H_2$), 24.8 (*C*$H_3$), 28.2 (*C*$H_2$), 29.0 (*C*$H_2$), 31.2 (*C*$H_2$), 35.7 (*C*$H_2$), 36.6 (t, *J* = 25.4 Hz, *C*$H_2$), 38.3 (t, *J* = 24.9 Hz, *C*$H_2$), 70.3 (*C*$H_2$), 72.8 (*C*$H_2$), 83.2 (*C*), 125.3 (t, *J* = 240.4 Hz, *C*$F_2$), 125.7 (*C*H), 127.4 (*C*H), 127.6 (*C*H), 128.30 (*C*H), 128.34 (*C*H), 138.6 (*C*), 142.2 (*C*). $^{19}$F NMR (373 MHz, $CDCl_3$): δ –98.1 to –95.4 (m, 2F). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{29}H_{41}{}^{11}BF_2O_3Na$, 509.3014; found, 509.3009.

**2-(6,6-Difluoro-10-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)decyl)isoindoline-1,3-dione (4ak).**

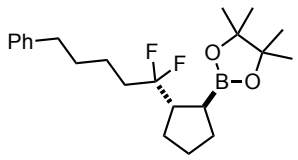



**4ak**

Prepared according to procedure **A** described above, except the catalyst loading {10 mol% of $[Cu(MeCN)_4]BF_4$ and 15 mol% of IMes•HCl was used.}. The reaction was conducted for 4 h with 52.6 mg (0.20 mmol) of **1a** and 174.7 mg (0.81 mmol) of **2o**. The product **4ak** was obtained in 28% yield (23.0 mg) with unidentified small amounts of byproducts.

$^1$H NMR (392 MHz, $CDCl_3$): δ 1.21 (s, 12H), 1.35–1.55 (m, 4H), 1.58–1.746 (m, 5H), 1.749–1.90 (m, 3H), 1.92–2.10 (m, 1H), 2.61 (t, *J* = 7.8 Hz, 2H), 3.67 (t, *J* = 7.1 Hz, 2H), 7.13–7.20 (m, 3H), 7.23–7.30 (m, 2H), 7.67–7.73 (m, 2H), 7.80–7.86 (m, 2H). $^{13}$C NMR (99 MHz, $CDCl_3$): δ 17.0 (br, B–*C*H), 22.0 (t, *J* = 4.7 Hz, *C*$H_2$), 24.7 (*C*$H_3$), 27.9 (*C*$H_2$), 28.9 (*C*$H_2$), 31.2 (*C*$H_2$), 35.7 (*C*$H_2$), 36.5 (t, *J* = 24.9 Hz, *C*$H_2$), 38.0 (*C*$H_2$), 38.2 (t, *J* = 25.4 Hz, *C*$H_2$), 83.3 (*C*), 123.1 (*C*H), 125.3 (t, *J* = 240.5 Hz, *C*$F_2$), 125.7 (*C*H), 128.27 (*C*H), 128.34 (*C*H), 132.1 (*C*), 133.8 (*C*H), 142.2 (*C*), 168.3 (*C*). $^{19}$F NMR (373 MHz, $CDCl_3$): δ –98.3 to –95.4 (m, 2F). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{30}H_{38}{}^{11}BF_2NO_4Na$, 548.2760; found, 548.2757.

**2-[(*trans*)-2-(1,1-Difluoro-5-phenylpentyl)cyclopentyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4al)**

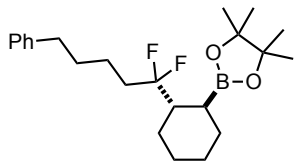



**4al**

Prepared according to procedure **A** described above, except the catalyst loading {10 mol% of $[Cu(MeCN)_4]BF_4$ and 15 mol% of IMes•HCl was used.}. The reaction was conducted for 4 h with 52.6 mg (0.20 mmol) of **1a** and 70.8 μL (0.80 mmol) of **2l**. The product **4al** was obtained in 44% yield (33.4 mg) with d.r. = >95:5.

$^1$H NMR (392 MHz, $CDCl_3$): δ 1.23 (s, 12H), 1.28–1.40 (m, 1H), 1.42–1.92 (m, 12H), 2.35–2.52 (m, 1H), 2.62 (t, $J$ = 7.6 Hz, 2H), 7.14–7.21 (m, 3H), 7.23–7.30 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 21.7 (t, $J$ = 3.8 Hz, $C$H$_2$), 22.7 (br, B–$C$H), 24.56 ($C$H$_3$), 24.63 ($C$H$_3$), 26.9 ($C$H$_2$), 27.5 ($C$H$_2$), 29.4 ($C$H$_2$), 31.4 ($C$H$_2$), 35.7 (t, $J$ = 25.4 Hz, $C$H$_2$), 35.8 ($C$H$_2$), 48.2 (t, $J$ = 24.0 Hz, $C$H), 83.1 ($C$), 125.7 ($C$H), 126.2 (t, $J$ = 243.4 Hz, $C$F$_2$), 128.27 ($C$H), 128.34 ($C$H), 142.3 ($C$). $^{19}$F NMR (373 MHz, $CDCl_3$): δ –106.5 to –105.6 (m, 1F), –103.8 to –102.9 (m, 1F). HRMS–ESI ($m/z$): $[M+Na]^+$ calcd for $C_{22}H_{33}O_2{}^{11}BF_2Na$, 401.2438; found, 401.2429.

**2-[(*trans*)-2-(1,1-Difluoro-5-phenylpentyl)cyclohexyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4am).**



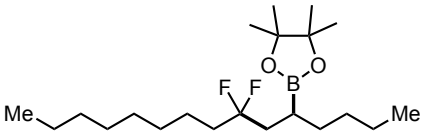

**4am**

Prepared according to procedure **A** described above, except the catalyst loading {10 mol% of $[Cu(MeCN)_4]BF_4$ and 15 mol% of IMes•HCl was used.}. The reaction was conducted for 5 h with 52.9 mg (0.20 mmol) of **1a** and 81.0 μL (0.80 mmol) of **2m**. The product **4am** was obtained in 18% yield (14.1 mg) with d.r. = >95:5. The relative stereochemistry of **4am** was determined by X-ray crystallographic analysis.

$^1$H NMR (392 MHz, $CDCl_3$): δ 0.92–1.33 (m, 6H), 1.22 (s, 12H), 1.57–2.04 (m, 10H), 2.62 (t, $J$ = 7.6 Hz, 2H), 7.12–7.21 (m, 3H), 7.22–7.31 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 21.5 ($C$H$_2$), 24.58 ($C$H$_3$), 24.63 ($C$H$_3$), 25.5 ($C$H$_2$), 26.3 ($C$H$_2$), 27.1 (t, $J$ = 4.3 Hz, $C$H$_2$), 27.5 ($C$H$_2$), 31.2 ($C$H$_2$), 33.4

(t, $J$ = 25.9 Hz, $C$H$_2$), 35.7 ($C$H$_2$), 44.7 (t, $J$ = 23.0 Hz, $C$H), 82.8 ($C$), 125.7 ($C$H), 126.7 (t, $J$ = 243.9 Hz, $C$F$_2$), 128.3 ($C$H), 128.4 ($C$H), 142.3 ($C$). The carbon directly attached to the boron atom was not detected. $^{19}$F NMR (373 MHz, CDCl$_3$): δ –104.6 to –103.7 (m, 1F), –99.2 to –98.3 (m, 1F). HRMS–ESI ($m/z$): [M+Na]$^+$ calcd for $C_{23}H_{35}O_2{}^{11}BF_2Na$, 415.2595; found, 415.2589.

**2-(7,7-Difluoropentadecan-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4fa).**

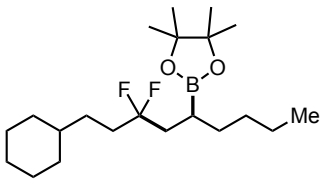



**4fa**

Prepared according to procedure **A** described above. The reaction was conducted for 4 h with 48.6 mg (0.20 mmol) of **1f** and 100.8 μL (0.80 mmol) of **2a**. The product **4fa** was obtained in 71% yield (53.3 mg).

$^1$H NMR (401 MHz, CDCl$_3$): δ 0.88 (t, $J$ = 6.8 Hz, 6H), 1.15–1.36 (m, 18H), 1.24 (s, 12H), 1.39–1.51 (m, 2H), 1.71–1.89 (m, 2H), 1.94–2.10 (m, 1H). $^{13}$C NMR (99 MHz, CDCl$_3$): δ 14.0 ($C$H$_3$), 14.1 ($C$H$_3$), 17.4 (br, B–$C$H), 22.3 (t, $J$ = 4.7 Hz, $C$H$_2$), 22.6 ($C$H$_2$), 22.8 ($C$H$_2$), 24.72 ($C$H$_3$), 24.74 ($C$H$_3$), 29.1 ($C$H$_2$), 29.36 ($C$H$_2$), 29.38 ($C$H$_2$), 31.1 ($C$H$_2$), 31.5 ($C$H$_2$), 31.8 ($C$H$_2$), 36.7 (t, $J$ = 25.5 Hz, $C$H$_2$), 38.4 (t, $J$ = 25.0 Hz, $C$H$_2$), 83.1 ($C$), 125.6 (t, $J$ = 241.2 Hz, $C$F$_2$). $^{19}$F NMR (369 MHz, CDCl$_3$): δ –97.7 to –95.5 (m, 2F). HRMS–ESI ($m/z$): [M+Na]$^+$ calcd for $C_{21}H_{41}O_2{}^{11}BF_2Na$, 397.3064; found, 397.3061.

**2-(1-Cyclohexyl-3,3-difluorononan-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4ga).**



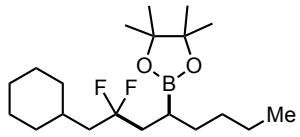

**4ga**

Prepared according to procedure **A** described above, except the catalyst loading {10 mol% of [Cu(MeCN)$_4$]BF$_4$ and 15 mol% of IMes•HCl was used.}. The reaction was conducted for 3 h with 49.0 mg (0.20 mmol) of **1g** and 100.8 μL (0.80 mmol) of **2a**. The product **4ga** was obtained in 69% yield (51.9 mg).

$^1$H NMR (392 MHz, CDCl$_3$): δ 0.81–0.97 (m, 2H), 0.88 (t, $J$ = 6.5 Hz, 3H), 1.07–1.51 (m, 13H), 1.24 (s, 12H), 1.60–1.90 (m, 8H), 1.92–2.10 (m, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 14.0 ($C$H$_3$), 17.3 (br, B–$C$H), 22.8 ($C$H$_2$), 24.7 ($C$H$_3$), 26.3 ($C$H$_2$), 26.6 ($C$H$_2$), 29.7 ($C$H$_2$), 31.1 ($C$H$_2$), 31.5 ($C$H$_2$), 33.1 (d, $J$ = 5.7 Hz, $C$H$_2$), 34.2 (t, $J$ = 25.4 Hz, $C$H$_2$), 37.4 ($C$H), 38.4 (t, $J$ = 25.4 Hz, $C$H$_2$), 83.1 ($C$),

125.8 (t, $J$ = 241.4 Hz, $C$F$_2$). $^{19}$F NMR (373 MHz, CDCl$_3$): δ –97.9 to –95.7 (m, 2F). HRMS–ESI ($m/z$): [M+Na]$^+$ calcd for $C_{21}H_{39}O_2{}^{11}BF_2Na$, 395.2907; found, 395.2904.

**2-(1-Cyclohexyl-2,2-difluorooctan-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4ha).**

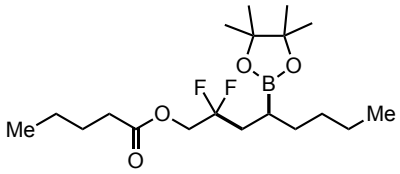



**4ha**

Prepared according to procedure **A** described above, except the catalyst loading {10 mol% of [Cu(MeCN)$_4$]BF$_4$ and 15 mol% of IMes•HCl was used.}. The reaction was conducted for 3 h with 45.4 mg (0.20 mmol) of **1h** and 100.8 μL (0.80 mmol) of **2a**. The product **4ha** was obtained in 63% yield (45.2 mg).

$^1$H NMR (392 MHz, CDCl$_3$): δ 0.88 (t, $J$ = 6.7 Hz, 3H), 0.92–1.03 (m, 2H), 1.07–1.50 (m, 11H), 1.24 (s, 12H), 1.58–1.89 (m, 8H), 1.94–2.12 (m, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 14.0 ($C$H$_3$), 17.3 (br, B–$C$H), 22.8 ($C$H$_2$), 24.7 ($C$H$_3$), 26.2 ($C$H$_2$), 31.1 ($C$H$_2$), 31.4 ($C$H$_2$), 32.4 ($C$H), 33.8 ($C$H$_2$), 34.0 ($C$H$_2$), 39.1 (t, $J$ = 25.4 Hz, $C$H$_2$), 43.9 (t, $J$ = 24.4 Hz, $C$H$_2$), 83.0 ($C$), 125.8 (t, $J$ = 242.4 Hz, $C$F$_2$). $^{19}$F NMR (373 MHz, CDCl$_3$): δ –94.9 to –92.8 (m, 2F). HRMS–ESI ($m/z$): [M+Na]$^+$ calcd for $C_{20}H_{37}O_2{}^{11}BF_2Na$, 381.2751; found, 381.2747.

**2,2-Difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)octyl pentanoate (4ia).**



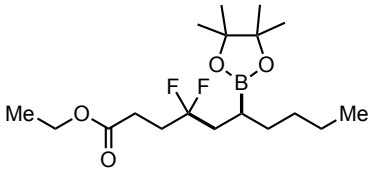

**4ia**

Prepared according to procedure **A** described above, except the catalyst loading {10 mol% of [Cu(MeCN)$_4$]BF$_4$ and 15 mol% of IMes•HCl was used.}. The reaction was conducted for 2 h with 50.4 mg (0.21 mmol) of **1i** and 125.2 μL (0.80 mmol) of **2b**. The product **4ia** was obtained in 59% yield (45.3 mg).

$^1$H NMR (399 MHz, CDCl$_3$): δ 0.88 (t, $J$ = 7.2 Hz, 3H), 0.92 (t, $J$ = 7.4 Hz, 3H), 1.23 (s, 12H), 1.25–1.52 (m, 10H), 1.59–1.68 (m, 2H), 1.82–2.17 (m, 1H), 2.38 (t, $J$ = 7.6 Hz, 2H), 4.24 (dd, $J$ = 8.0, 13.6 Hz, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 13.6 ($C$H$_3$), 13.9 ($C$H$_3$), 16.9 (br, B–$C$H), 22.2 ($C$H$_2$), 22.7 ($C$H$_2$), 24.68 ($C$H$_3$), 24.74 ($C$H$_3$), 26.9 ($C$H$_2$), 31.0 ($C$H$_2$), 31.3 ($C$H$_2$), 33.6 ($C$H$_2$), 35.7 (t, $J$ = 23.5 Hz, $C$H$_2$), 63.8 (t, $J$ = 33.1 Hz, $C$H$_2$), 83.2 ($C$), 121.8 (t, $J$ = 243.4 Hz, $C$F$_2$), 172.7 ($C$). $^{19}$F NMR

(373 MHz, $CDCl_3$): δ –106.3 to –103.2 (m, 2F). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{19}H_{35}O_4{}^{11}BF_2$, 399.2492; found, 399.2489.

**2,2-Difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)octyl pentanoate (4ja).**

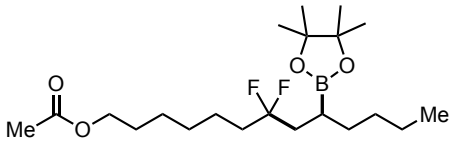



**4ja**

Prepared according to procedure **A** described above, except the catalyst loading {10 mol% of $[Cu(MeCN)_4]BF_4$ and 15 mol% of IMes•HCl was used.}. The reaction was conducted for 4 h with 46.2 mg (0.20 mmol) of **1j** and 100.8 μL (0.80 mmol) of **2a**. The product **4ja** was obtained in 42% yield (30.5 mg).

$^1H$ NMR (392 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.9 Hz, 3H), 1.15–1.37 (m, 11H), 1.24 (s, 12H), 1.75–1.91 (m, 1H), 1.97–2.28 (m, 2H), 2.50 (t, *J* = 7.8 Hz, 2H), 4.14 (q, *J* = 4.8 Hz, 2H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 14.0 (*C*$H_3$), 14.2 (*C*$H_3$), 17.2 (br, B–*C*H), 22.8 (*C*$H_2$), 24.70 (*C*$H_3$), 24.75 (*C*$H_3$), 27.4 (t, *J* = 4.3 Hz, *C*$H_2$), 31.0 (*C*$H_2$), 31.4 (*C*$H_2$), 32.0 (t, *J* = 25.9 Hz, *C*$H_2$), 38.6 (t, *J* = 24.5 Hz, *C*$H_2$), 60.6 (*C*$H_2$), 83.2 (*C*), 124.5 (t, *J* = 242.4 Hz, *C*$F_2$), 172.5 (*C*). $^{19}F$ NMR (373 MHz, $CDCl_3$): δ –99.9 to –97.8 (m, 2F). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{18}H_{33}O_4{}^{11}BF_2Na$, 385.2336; found, 385.2331.

**7,7-Difluoro-9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)tridecyl acetate (4ka).**



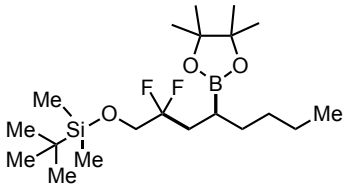

**4ka**

Prepared according to procedure **A** described above, except the catalyst loading {10 mol% of $[Cu(MeCN)_4]BF_4$ and 15 mol% of IMes•HCl was used.}. The reaction was conducted for 3 h with 53.0 mg (0.19 mmol) of **1k** and 100.0 μL (0.80 mmol) of **2a**. The product **4ka** was obtained in 69% yield (54.6 mg).

$^1H$ NMR (401 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7.2 Hz, 3H), 1.16–1.40 (m, 10H), 1.24 (s, 12H), 1.42–1.51 (m, 2H), 1.59–1.67 (m, 3H), 1.73–1.90 (m, 3H), 1.94–2.10 (m, 1H), 2.05 (s, 3H), 4.05 (t, *J* = 6.6 Hz, 2H). $^{13}C$ NMR (99 MHz, $CDCl_3$): δ 14.0 (*C*$H_3$), 17.3 (br, B–*C*H), 21.0 (*C*$H_3$), 22.2 (t, *J* = 4.7 Hz, *C*$H_2$), 22.8 (*C*$H_2$), 24.70 (*C*$H_3$), 24.73 (*C*$H_3$), 25.7 (*C*$H_2$), 28.4 (*C*$H_2$), 29.0 (*C*$H_2$), 31.1 (*C*$H_2$), 31.4 (*C*$H_2$), 36.6 (t, *J* = 25.5 Hz, *C*$H_2$), 38.4 (t, *J* = 25.0 Hz, *C*$H_2$), 64.4 (*C*$H_2$), 83.1 (*C*), 125.4 (t, *J* = 241.7

Hz, $CF_2$), 171.2 (*C*). $^{19}F$ NMR (373 MHz, $CDCl_3$): δ –98.2 to –95.4 (m, 2F). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{21}H_{39}O_4{}^{11}BF_2Na$, 427.2806; found, 427.2800.

***tert*-Butyl{[2,2-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2 yl)octyl]oxy}dimethylsilane (4la).**

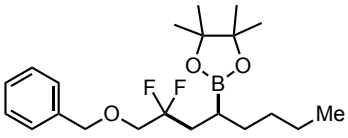



**4la**

Prepared according to procedure **A** described above, except the catalyst loading {10 mol% of $[Cu(MeCN)_4]BF_4$ and 15 mol% of IMes•HCl was used.}. The reaction was conducted for 5 h with 55.0 mg (0.20 mmol) of **1l** and 100.8 μL (0.80 mmol) of **2a**. The product **4la** was obtained in 57% yield (46.6 mg).

$^1H$ NMR (396 MHz, $CDCl_3$): δ 0.07 (s, 6H), 0.81–0.97 (m, 12H), 1.24 (s, 12H), 1.27–1.52 (m, 8H), 1.84–2.15 (m, 1H), 3.65–3.79 (m, 2H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ –5.52 ($CH_3$), –5.50 ($CH_3$), 14.0 ($CH_3$), 16.7 (br, B–*C*H), 18.2 (*C*), 22.7 ($CH_2$), 24.67 ($CH_3$), 24.72 ($CH_3$), 25.7 ($CH_3$), 31.1 ($CH_2$), 31.4 ($CH_2$), 34.9 (t, *J* = 24.2 Hz, $CH_2$), 64.5 (t, *J* = 34.5 Hz, $CH_2$), 83.0 (*C*), 123.7 (t, *J* = 248.4 Hz, $CF_2$). $^{19}F$ NMR (373 MHz, $CDCl_3$): δ –108.3 to –107.4 (m, 1F), –104.7 to –103.8 (m, 1F). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{20}H_{41}O_3{}^{11}BF_2NaSi$, 429.2782; found, 429.2779.

**2-[1-(Benzyloxy)-2,2-difluorooctan-4-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4ma).**



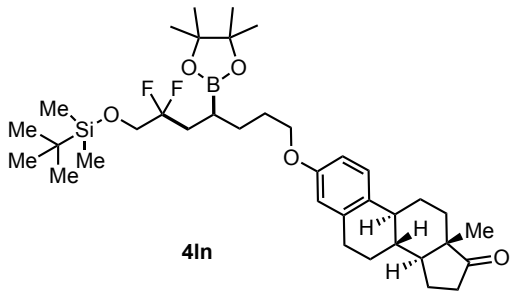

**4ma**

Prepared according to procedure **A** described above, except the catalyst loading {10 mol% of $[Cu(MeCN)_4]BF_4$ and 15 mol% of IMes•HCl was used.}. The reaction was conducted for 2 h with 51.5 mg (0.21 mmol) of **1m** and 100.8 μL (0.80 mmol) of **2a**. The product **4ma** was obtained in 28% yield (21.8 mg).

$^1H$ NMR (392 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.9 Hz, 3H), 1.23 (s, 12H), 1.25–1.52 (m, 8H), 1.89–2.19 (m, 1H), 3.53–3.72 (m, 2H), 4.55–4.65 (m, 2H), 7.27–7.40 (m, 5H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 14.0 ($CH_3$), 16.7 (br, B–*C*H), 22.8 ($CH_2$), 24.69 ($CH_3$), 24.75 ($CH_3$), 31.1 ($CH_2$), 31.4 ($CH_2$), 35.6 (t, *J* = 23.5 Hz, $CH_2$), 70.7 (t, *J* = 32.1 Hz, $CH_2$), 73.7 ($CH_2$), 83.1 (*C*), 123.4 (t, *J* = 243.9 Hz, $CF_2$),

127.7 (*C*H), 127.8 (*C*H), 128.4 (*C*H), 137.4 (*C*). $^{19}$F NMR (369 MHz, $CDCl_3$): δ –105.6 to –101.6 (m, 2F). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{21}H_{33}O_3{}^{11}BF_2Na$, 405.2387; found, 405.2381.

**(8*R*,9*S*,13*S*,14*S*)-3-({7-[(*tert*-Butyldimethylsilyl)oxy]-6,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)heptyl}oxy)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (4ln).**

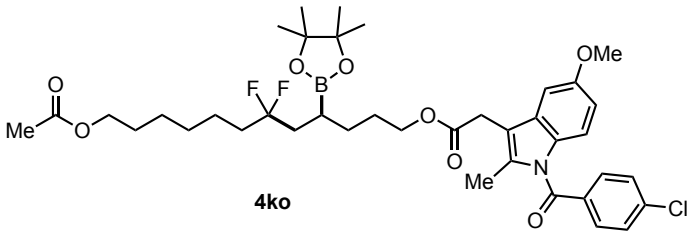



**4ln**

Prepared according to procedure **A** described above, except the catalyst loading {10 mol% of $[Cu(MeCN)_4]BF_4$ and 15 mol% of IMes•HCl was used.} with 1,4-dioxane/DMF (500 μL/150 μL). The reaction was conducted for 4 h with 56.5 mg (0.21 mmol) of **1l** and 270.7 mg (0.80 mmol) of **2n**. The product **4ln** was obtained in 33% yield (44.2 mg).

$^1$H NMR (392 MHz, $CDCl_3$): δ 0.07 (s, 6H), 0.90 (s, 9H), 0.91 (s, 3H), 1.20–1.35 (m, 3H), 1.23 (s, 12H), 1.37–1.69 (m, 6H), 1.72–1.84 (m, 2H), 1.92–2.20 (m, 6H), 2.21–2.29 (m, 1H), 2.35–2.44 (m, 1H), 2.50 (dd, *J* = 5.6, 19.0 Hz, 1H), 2.82–2.92 (m, 2H), 3.65–3.77 (m, 2H), 3.92 (t, *J* = 6.5 Hz, 2H), 6.63 (d, *J* = 2.7 Hz, 1H), 6.70 (dd, *J* = 1.7, 8.6 Hz, 1H), 7.18 (d, *J* = 8.6 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ –5.49 (*C*$H_3$), 13.8 (*C*$H_3$), 16.5 (br, B–*C*H), 18.2 (*C*), 21.6 (*C*$H_2$), 24.7 (*C*$H_3$), 25.7 (*C*$H_3$), 25.9 (*C*$H_2$), 26.6 (*C*$H_2$), 28.1 (*C*$H_2$), 28.6 (*C*$H_2$), 29.6 (*C*$H_2$), 31.6 (*C*$H_2$), 34.8 (t, *J* = 23.5 Hz, *C*$H_2$), 35.8 (*C*$H_2$), 38.4 (*C*H), 44.0 (*C*H), 48.0 (*C*), 50.4 (*C*H), 64.6 (t, *J* = 34.5 Hz, *C*$H_2$), 67.8 (*C*$H_2$), 83.2 (*C*), 112.2 (*C*H), 114.5 (*C*H), 123.6 (t, *J* = 243.3 Hz, *C*$F_2$), 126.2 (*C*H), 131.8 (*C*), 137.6 (*C*), 157.0 (*C*), 220.9 (*C*). $^{19}$F NMR (369 MHz, $CDCl_3$): δ –108.2 to –104.2 (m, 2F). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{37}H_{59}O_5{}^{11}BF_2NaSi$, 683.4092; found, 683.4083.

**11-Acetoxy-5,5-difluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)undecyl 2-[1-(4-chlorobenzoyl)-2-methyl-1*H*-indol-3-yl]acetate (4ko).**

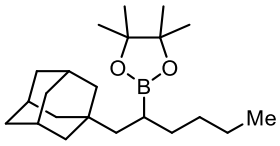


**4ko**

Prepared according to procedure **A** described above, except the catalyst loading {10 mol% of $Cu(MeCN)_4BF_4$ and 15 mol% of IMes•HCl was used.} with 1,4-dioxane/DMF (500 μL/150 μL). The reaction was conducted for 4 h with 54.4 mg (0.20 mmol) of **1a** and 344.9 mg (0.81 mmol) of **2b**. The product **4ko** was obtained in 25% yield (37.3 mg) with unidentified small amounts of byproducts.

$^1$H NMR (396 MHz, $CDCl_3$): δ 1.21 (s, 12H), 1.31–1.51 (m, 8H), 1.59–1.68 (m, 5H), 1.69–1.86 (m, 3H), 1.88–2.08 (m, 1H), 2.05 (s, 3H), 2.39 (s, 3H), 3.65 (s, 2H), 3.83 (s, 3H), 4.07 (dt, *J* = 2.7, 10.5 Hz, 4H,), 6.66 (dd, *J* = 2.8, 9.1 Hz, 1H), 6.85 (d, *J* = 9.1 Hz, 1H), 6.96 (d, *J* = 2.4 Hz, 1H), 7.48 (d, *J* = 7.1 Hz, 2H), 7.67 (d, *J* = 8.7 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 13.3 (*C*$H_3$), 16.9 (br, B–*C*H), 21.0 (*C*$H_3$), 22.1 (t, *J* = 3.8 Hz, *C*$H_2$), 24.7 (*C*$H_3$), 25.7 (*C*$H_2$), 27.88 (*C*$H_2$), 27.91 (*C*$H_2$), 28.4 (*C*$H_2$), 28.9 (*C*$H_2$), 30.3 (*C*$H_2$), 36.7 (t, *J* = 25.2 Hz, *C*$H_2$), 38.2 (t, *J* = 24.8 Hz, *C*$H_2$), 55.6 (*C*$H_3$), 64.4 (*C*$H_2$), 65.0 (*C*$H_2$), 83.2 (*C*), 101.2 (*C*H), 111.6 (*C*H), 112.7 (*C*), 114.9 (*C*H), 125.2 (t, *J* = 240.7 Hz, *C*$F_2$), 129.1 (*C*H), 130.6 (*C*), 130.7 (*C*), 131.1 (*C*H), 133.9 (*C*), 135.9 (*C*), 139.2 (*C*), 156.0 (*C*), 168.2 (*C*), 170.8 (*C*), 171.2 (*C*). $^{19}$F NMR (373 MHz, $CDCl_3$): δ –98.5 to –96.1 (m, 2F). HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{39}H_{51}{}^{11}BClF_2NO_8$, 745.3371; found, 745.3377.

**2-{1-[(3r,5r,7r)-Adamantan-1-yl]hexan-2-yl}-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4ca).**

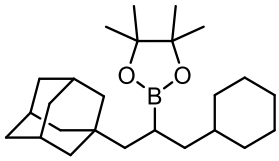


**4ca**

Prepared according to procedure **B** described above. The reaction was conducted for 2 h with 43.1 mg (0.20 mmol) of **1c** and 100.5 μL (0.80 mmol) of **2a**. The product **4ca** was obtained in 71% yield (49.0 mg).

$^1$H NMR (401 MHz, $CDCl_3$): δ 0.87 (t, *J* = 4.8 Hz, 3H), 0.93–1.04 (m, 2H), 1.19–1.31 (m, 5H), 1.24 (s, 6H), 1.25 (s, 6H), 1.34–1.53 (m, 8H), 1.62–1.76 (m, 6H), 1.87–1.96 (m, 3H). $^{13}$C NMR (99 MHz, $CDCl_3$): δ 14.0 (*C*$H_3$), 16.9 (br, B–*C*H), 22.9 (*C*$H_2$), 24.8 (*C*$H_3$), 24.9 (*C*$H_3$), 28.8 (*C*H), 31.3 (*C*$H_2$), 32.8 (*C*), 33.3 (*C*$H_2$), 37.2 (*C*$H_2$) 42.7 (*C*$H_2$), 46.6 (*C*$H_2$), 82.7 (*C*). HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{22}H_{40}O_2{}^{11}B$, 347.3120; found, 347.3117.

**2-{1-[(3r,5r,7r)-Adamantan-1-yl]-3-cyclohexylpropan-2-yl}-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4cc).**

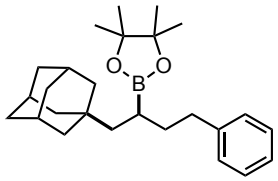


**4cc**

Prepared according to procedure **B** described above. The reaction was conducted for 2 h with 43.3 mg (0.20 mmol) of **1c** and 122.2 μL (0.80 mmol) of **2c**. The product **4cc** was obtained in 54% yield (42.2 mg).

$^{1}$H NMR (401 MHz, $CDCl_3$): δ 0.75–0.90 (m, 2H), 0.95–1.36 (m, 11H), 1.24 (s, 6H), 1.25 (s, 6H), 1.37–1.52 (m, 7H), 1.59–1.69 (m, 8H), 1.88–1.96 (m, 3H). $^{13}$C NMR (99 MHz, $CDCl_3$): δ 13.9 (br, B–*C*H), 24.8 (*C*$H_3$), 26.45 (*C*$H_2$), 26.50 (*C*$H_2$), 26.7 (*C*$H_2$), 28.8 (*C*H), 32.9 (*C*), 33.5 (*C*$H_2$), 33.7 (*C*$H_2$), 36.7 (*C*H), 37.2 (*C*$H_2$), 41.2 (*C*$H_2$), 42.7 (*C*$H_2$), 46.7 (*C*$H_2$), 82.7(*C*). HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{25}H_{43}O_2{}^{11}B$, 386.3361; found, 386.3350.

**2-{1-[(3r,5r,7r)-Adamantan-1-yl]-4-phenylbutan-2-yl}4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4cd).**

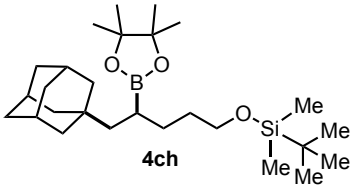


**4cd**

Prepared according to procedure **B** described above. The reaction was conducted for 4 h with 43.0 mg (0.20 mmol) of **1c** and 120.2 μL (0.80 mmol) of **2d**. The product **4cd** was obtained in 71% yield (56.1 mg).

$^{1}$H NMR (396 MHz, $CDCl_3$): δ 1.00–1.13 (m, 2H), 1.26 (s, 6H), 1.27 (s, 6H), 1.38–1.77 (m, 15H), 1.88–1.96 (m, 3H), 2.53–2.68 (m, 2H), 7.12–7.21 (m, 3H), 7.23–7.31 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 17.2 (br, B–*C*H), 24.8 (*C*$H_3$), 24.9 (*C*$H_3$), 28.7 (*C*H), 32.8 (*C*), 35.5 (*C*$H_2$), 35.7 (*C*$H_2$), 37.2 (*C*$H_2$), 42.7 (*C*$H_2$) 46.4 (*C*$H_2$), 82.9 (*C*), 125.5 (*C*H), 128.2 (*C*H), 128.3 (*C*H), 143.0 (*C*). HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{26}H_{39}O_2{}^{11}B$, 394.3048; found, 394.3036.

**({6-[(3r,5r,7r)-Adamantan-1-yl]-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexyl}oxy)(tert-butyl)dimethylsilane (4ch).**

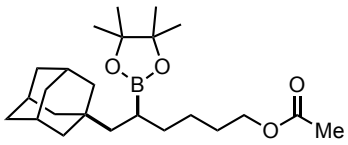


**4ch**

Prepared according to procedure **B** described above. The reaction was conducted for 4 h with 43.0 mg (0.20 mmol) of **1c** and 197.5 μL (0.80 mmol) of **2h**. The product **4ch** was obtained in 67% yield (61.3 mg).

$^{1}$H NMR (401 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.89 (s, 9H), 0.92–1.06 (m, 2H), 1.24 (s, 6H), 1.25 (s, 6H), 1.34–1.76 (m, 17H), 1.86–1.96 (m, 3H), 3.58 (t, $J$ = 6.4 Hz, 2H). $^{13}$C NMR (99 MHz, $CDCl_3$): δ –5.3 (*C*H), 16.7 (br, B–*C*H), 18.3 (*C*), 24.8 (*C*$H_3$), 24.9 (*C*$H_3$), 26.0 (*C*$H_3$), 28.7 (*C*$H_3$), 29.6 (*C*$H_2$), 32.3 (*C*$H_2$), 32.8 (*C*), 37.2 (*C*$H_2$), 42.7 (*C*$H_2$), 46.5 (*C*$H_2$), 63.5 (*C*$H_2$), 82.8 (*C*). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{27}H_{51}{}^{11}BO_3SiNa$, 485.3598; found, 485.3596.

**6-[(3r,5r,7r)-Adamantan-1-yl]-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexyl acetate (4ci).**

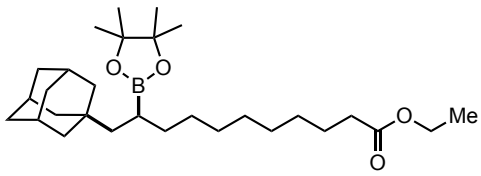


**4ci**

Prepared according to procedure **B** described above. The reaction was conducted for 5 h with 43.1 mg (0.20 mmol) of **1c** and 113.7 μL (0.80 mmol) of **2i**. The product **4ci** was obtained in 62% yield (50.4 mg).

$^{1}$H NMR (401 MHz, $CDCl_3$): δ 0.94–1.03 (m, 2H), 1.24 (s, 6H), 1.25 (s, 6H), 1.34–1.53 (m, 11H), 1.59–1.72 (m, 8H), 1.88–1.95 (m, 3H), 2.03 (s, 3H), 4.04 (t, $J$ = 6.6 Hz, 2H). $^{13}$C NMR (99 MHz, $CDCl_3$): δ 17.0 (br, B–*C*H), 21.0 (*C*$H_2$), 24.8 (*C*$H_3$), 24.9 (*C*$H_3$), 25.3 (*C*$H_2$), 28.7 (*C*H), 28.8 (*C*$H_2$), 32.8 (*C*), 33.2 (*C*$H_2$), 37.2 (*C*$H_2$) 42.6 (*C*$H_2$), 46.5 (*C*$H_2$), 64.6 (*C*$H_2$), 82.8 (*C*), 171.2 (*C*). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{24}H_{41}{}^{11}BO_4Na$, 427.2995; found, 427.2993.

**Ethyl 11-[(3r,5r,7r)-adamantan-1-yl]-10-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)undecanoate (4cp).**

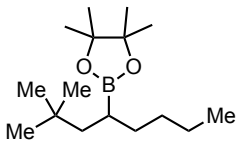



**4cp**

Prepared according to procedure **B** described above. The reaction was conducted for 4 h with 43.6 mg (0.20 mmol) of **1c** and 193.0 μL (0.80 mmol) of **2p**. The product **4cp** was obtained in 63% yield (60.3 mg).

$^{1}$H NMR (392 MHz, $CDCl_3$): δ 0.92–1.03 (m, 2H), 1.22–1.30 (m, 12H), 1.235 (s, 6H), 1.244 (s, 6H), 1.33–1.53 (m, 9H), 1.58–1.72 (m, 9H), 1.88–1.95 (m, 3H), 2.28 (t, $J$ = 7.6 Hz, 2H), 4.12 (q, $J$ = 4.8 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 14.2 (*C*H$_3$), 17.0 (br, B–*C*H), 24.8 (*C*H$_3$), 24.9 (*C*H$_3$), 25.0 (*C*H$_2$), 28.7 (*C*H), 29.0 (*C*H$_2$), 29.1 (*C*H$_2$), 29.2 (*C*H$_2$), 29.3 (*C*H$_2$), 29.8 (*C*H$_2$), 32.8 (*C*), 33.6 (*C*H$_2$), 34.4 (*C*H$_2$), 37.2 (*C*H$_2$), 42.6 (*C*H$_2$), 46.6 (*C*H$_2$), 60.1 (*C*H$_2$), 82.7 (*C*), 173.9 (*C*). HRMS–EI (*m*/*z*): [M]$^+$ calcd for $C_{29}H_{51}O_4{}^{11}B$, 474.3886; found, 474.3882.

**2-(2,2-Dimethyloctan-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4pa).**

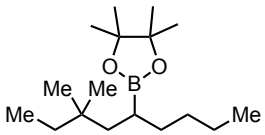



**4pa**

Prepared according to procedure **A** described above, except the catalyst loading {10 mol% of $[Cu(MeCN)_4]BF_4$ and 15 mol% of IMes•HCl was used.}. The reaction was conducted for 2 h with 54.8 mg (0.40 mmol) of **1p** and 201.0 μL (1.60 mmol) of **2a**. The product **4pa** was purified by GPC and obtained in 32% yield (33.9 mg).

$^{1}$H NMR (396 MHz, $CDCl_3$): δ 0.80–0.98 (m, 14H), 1.236 (s, 6H), 1.244 (s, 6H), 1.25–1.44 (m, 6H), 1.49–1.54 (m, 1H). $^{13}$C NMR (99 MHz, $CDCl_3$): δ 14.0 (*C*H$_3$), 19.2 (br, B–*C*H), 23.0 (*C*H$_2$), 24.8 (*C*H$_3$), 24.9 (*C*H$_3$), 29.7 (*C*H$_3$), 31.0 (*C*), 31.3 (*C*H$_2$), 33.3 (*C*H$_2$), 45.9 (*C*H$_2$), 82.7 (*C*). HRMS–EI (*m*/*z*): [M]$^+$ calcd for $C_{16}H_{33}O_2{}^{10}B$, 267.2610; found, 267.2620.

**2-(3,3-Dimethylnonan-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4qa).**

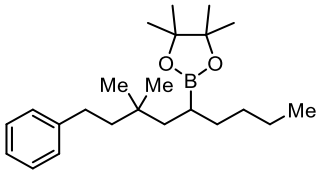


**4qa**

Prepared according to procedure **A** described above, except the catalyst loading {10 mol% of $[Cu(MeCN)_4]BF_4$ and 15 mol% of IMes•HCl was used.}. The reaction was conducted for 4 h with 60.4 mg (0.40 mmol) of **1q** and 201.0 μL (0.80 mmol) of **2a**. The product **4qa** was purified by GPC and obtained in 35% yield (39.8 mg).

$^1$H NMR (392 MHz, $CDCl_3$): δ 0.76–0.83 (m, 9H), 0.87 (t, $J$ = 6.7 Hz, 3H), 0.90–0.97 (m, 1H), 1.10–1.44 (m, 9H), 1.236 (s, 6H), 1.244 (s, 6H), 1.49 (dd, $J$ = 6.9, 13.8 Hz, 1H). $^{13}$C NMR (99 MHz, $CDCl_3$): δ 8.4 ($CH_3$), 14.0 ($CH_3$), 18.7 (br, B–$CH$), 23.0 ($CH_2$), 24.8 ($CH_3$), 24.9 ($CH_3$), 26.67 ($CH_3$), 26.72 ($CH_3$), 31.3 ($CH_2$), 33.3 ($C$), 33.4 ($CH_2$), 34.5 ($CH_2$), 43.7 ($CH_2$), 82.7 ($C$). HRMS–ESI ($m/z$): $[M+H]^+$ calcd for $C_{17}H_{36}O_2{}^{11}B$, 283.2812; found, 283.2816

**2-(3,3-Dimethyl-1-phenylnonan-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4ra).**

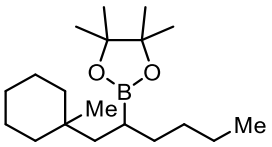


**4ra**

Prepared according to procedure **A** described above, except the catalyst loading {10 mol% of $[Cu(MeCN)_4]BF_4$ and 15 mol% of IMes•HCl was used.}. The reaction was conducted for 3 h with 90.7 mg (0.40 mmol) of **2r** and 201.0 μL (1.6 mmol) of **2a**. The product **4ra** was obtained in 26% yield (37.1 mg).

$^1$H NMR (392 MHz, $CDCl_3$): δ 0.88 (t, $J$ = 6.9 Hz, 3H), 0.91 (s, 3H), 0.92 (s, 3H), 0.94–1.06 (m, 2H), 1.19 (s, 6H), 1.20 (s, 6H), 1.24–1.34 (m, 6H), 1.37–1.62 (m, 3H), 2.53 (t, $J$ = 8.6 Hz, 2H), 7.12–7.20 (m, 3H), 7.22–7.28 (m, 2H). $^{13}$C NMR (99 MHz, $CDCl_3$): δ 14.0 ($CH_3$), 18.7 (br, B–$CH$), 23.0 ($CH_2$), 24.8 ($CH_3$), 27.0 ($CH_3$), 27.2 ($CH_3$), 30.9 ($CH_2$), 31.3 ($CH_2$), 33.4 ($CH_2$), 33.6 ($C$), 44.2 ($CH_2$), 44.9 ($CH_2$), 82.8 ($C$), 125.4 ($CH$), 128.2 ($CH$), 128.4 ($CH$), 143.7 ($C$). HRMS–EI ($m/z$): $[M]^+$ calcd for $C_{23}H_{39}O_2{}^{11}B$, 358.3047; found, 358.3040.

**4,4,5,5-Tetramethyl-2-[1-(1-methylcyclohexyl)hexan-2-yl]-1,3,2-dioxaborolane (4sa).**

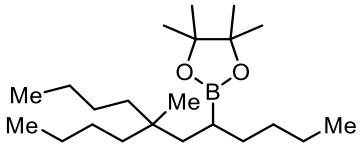



**4sa**

Prepared according to procedure **A** described above, except the catalyst loading {10 mol% of $[Cu(MeCN)_4]BF_4$ and 15 mol% of IMes•HCl was used.}. The reaction was conducted for 4 h with 70.6 mg (0.40 mmol) of **1s** and 201.0 μL (1.6 mmol) of **2a**. The product **4sa** was obtained in 24% yield (29.7 mg).

$^1$H NMR (401 MHz, $CDCl_3$): δ 0.83 (s, 3H), 0.87 (t, $J$ = 7.0 Hz, 3H), 0.91–0.98 (m, 1H), 1.15–1.30 (m, 10H), 1.23 (s, 6H), 1.25 (s, 6H), 1.34–1.47 (m, 6H), 1.49–1.55 (m, 2H). $^{13}$C NMR (99 MHz, $CDCl_3$): δ 14.0 ($CH_3$), 17.9 (br, B–$CH$), 22.2 ($CH_2$), 23.0 ($CH_2$), 24.8 ($CH_3$), 24.9 ($CH_3$), 26.6 ($CH_2$), 31.3 ($CH_2$), 33.2 ($C$), 33.4 ($CH_2$), 38.0 ($CH_2$), 44.8 ($CH_2$), 82.7 ($C$). HRMS–EI ($m/z$): $[M]^+$ calcd for $C_{19}H_{37}{}^{11}BO_2$, 308.2890; found, 308.2901.

**2-(7-Butyl-7-methylundecan-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4ta).**



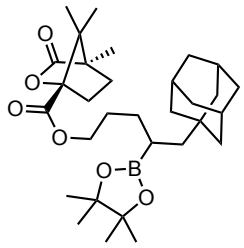

**4ta**

Prepared according to procedure **A** described above, except the catalyst loading {10 mol% of $[Cu(MeCN)_4]BF_4$ and 15 mol% of IMes•HCl were used.}. The reaction was conducted for 3 h with 88.0 mg (0.40 mmol) of **1t** and 201.0 μL (1.6 mmol) of **2a**. The product **4ta** was obtained in 21% yield (29.4 mg).

$^1$H NMR (396 MHz, $CDCl_3$): δ 0.77 (s, 3H), 0.84–0.91 (m, 9H), 1.09–1.18 (m, 9H), 1.20–1.41 (m, 11H), 1.24 (s, 6H), 1.25 (s, 6H), 1.46 (dd, $J$ = 10.5, 13.7 Hz, 1H). $^{13}$C NMR (99 MHz, $CDCl_3$): δ 14.0 ($CH_3$), 14.3 ($CH_3$), 18.0 (br, B–$CH$), 23.0 ($CH_2$), 23.7 ($CH_2$), 24.70 ($CH_3$), 24.73 ($CH_3$), 24.8 ($CH_3$), 24.9 ($CH_3$), 25.1 ($CH_3$), 25.90 ($CH_2$), 25.96 ($CH_2$), 31.3 ($CH_2$), 33.6 ($CH_2$), 35.5 ($C$), 39.1 ($CH_2$), 39.3 ($CH_2$), 42.1 ($CH_2$), 82.7 ($C$). HRMS–ESI ($m/z$): $[M+H]^+$ calcd for $C_{22}H_{46}O_2{}^{11}B$, 353.3589; found, 353.3585.

**5-[(3*R*,5*R*)-Adamantan-1-yl]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentyl (1*S*,4*R*)-**

**4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylate (4cq).**

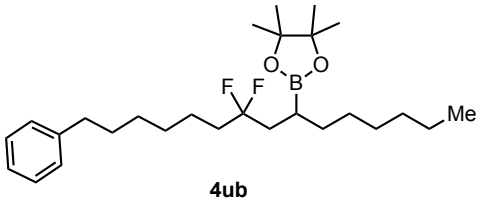


**4cq**

Prepared according to procedure **B** described above. The reaction was conducted for 4 h with 43.1 mg (0.20 mmol) of **1c** and 213.0 mg (0.80 mmol) of **2q**. The product **4cq** was purified by GPC and obtained in 52% yield (55.5 mg).

$^{1}$H NMR (396 MHz, $CDCl_3$): δ 0.96 (s, 3H), 0.98–1.03 (m, 2H), 1.05 (s, 3H), 1.12 (s, 3H), 1.235 (s, 6H), 1.243 (s, 6H), 1.36–1.52 (m, 8H), 1.56–1.78 (m, 10H), 1.87–1.97 (m, 4H), 2.03 (ddd, $J$ = 4.6, 9.4, 13.8 Hz, 1H), 2.42 (ddd, $J$ = 3.4, 9.9, 14.2 Hz, 1H), 4.15–4.27 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 9.7 ($CH_3$), 16.5 (br, B–*C*H), 16.7 ($CH_3$), 16.8 ($CH_3$), 24.76 ($CH_3$), 24.85 ($CH_3$), 28.0 (*C*), 28.6 (*C*H), 28.9 ($CH_2$), 29.59 ($CH_2$), 29.63 ($CH_2$), 30.6 ($CH_2$), 32.7 ($CH_2$), 37.1 ($CH_2$), 42.6 ($CH_2$), 46.3 ($CH_2$), 54.0 (*C*), 54.7 (*C*), 65.9 ($CH_2$), 82.9 (*C*), 91.1 (*C*), 167.4 (*C*) , 178.1 (*C*). HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{31}H_{49}O_6{}^{11}B$, 528.3628; found, 528.3612.

**2-[1-(Benzyloxy)-2,2-difluorooctan-4-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4ub).**

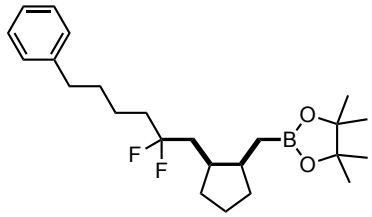


**4ub**

Prepared according to procedure **A** described above, except the catalyst loading {10 mol% of $[Cu(MeCN)_4]BF_4$ and 15 mol% of IMes•HCl were used.}. The reaction was conducted for 3 h with 114.7 mg (0.39 mmol) of **1u** and 251.1 μL (0.80 mmol) of **2b**. The product **4ub** was obtained in 74% yield (131.9 mg).

$^{1}$H NMR (396 MHz, $CDCl_3$): δ 0.87 (t, $J$ = 6.7 Hz, 3H), 1.21–1.38 (m, 15H), 1.23 (s, 12H), 1.40–1.51 (m, 3H), 1.59–1.67 (m, 2H), 1.71–1.88 (m, 2H), 1.93–2.10 (m, 1H), 2.60 (t, $J$ = 7.7 Hz, 2H), 7.14–7.21 (m, 3H), 7.24–7.31 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 14.0 ($CH_3$), 17.3 (br, B–*C*H), 22.3 (t, $J$ = 4.3 Hz, *C*$H_2$), 22.6 ($CH_2$), 24.70 ($CH_3$), 24.73 ($CH_3$), 28.8 ($CH_2$), 29.0 ($CH_2$), 29.2 ($CH_2$), 29.4 ($CH_2$), 29.6 ($CH_2$), 31.3 ($CH_2$), 31.7 ($CH_2$), 31.8 ($CH_2$), 35.9 ($CH_2$), 36.7 (t, $J$ = 25.4 Hz, *C*$H_2$), 38.4 (t, $J$ = 24.9 Hz, *C*$H_2$), 83.0 (*C*), 125.5 (t, $J$ = 241.5 Hz, *C*$F_2$), 125.6 (*C*H), 128.2 (*C*H), 128.3 (*C*H), 142.7 (*C*). $^{19}$F NMR (369 MHz, $CDCl_3$): δ –97.7 to –95.1 (m, 2F). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{27}H_{45}O_2{}^{11}BF_2Na$, 473.3378; found, 473.3373.

**2-{[2-(2,2-Difluoro-6-phenylhexyl)cyclopentyl]methyl}-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (7a).**

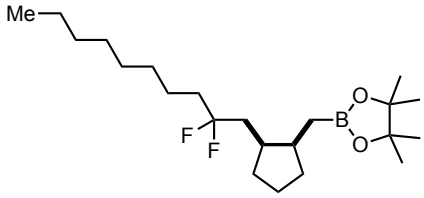



**7a**

Prepared according to procedure **A** described above, except the catalyst loading {10 mol% of $Cu(MeCN)_4BF_4$ and 15 mol% of IMes•HCl was used.}. The reaction was conducted for 2 h with 53.2 mg (0.20 mmol) of **1a** and 108.4 μL (0.80 mmol) of **2r**. The product **7a** was obtained in 79% yield (64.6 mg) with *cis*:*trans* = 83:17, which was determined by GC-analysis of the crude reaction mixture.

$^1$H NMR (401 MHz, $CDCl_3$): δ 0.51–0.81 (m, 2H), 1.17–1.53 (m, 6H), 1.24 (s, 12H), 1.60–2.20 (m, 10H), 2.62 (d, $J$ = 7.6 Hz, 2H), 7.14–7.21 (m, 3H), 7.23–7.31 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 11.5 (br, B–$CH_2$), 22.1 (t, $J$ = 4.8 Hz, $CH_2$), 22.3 ($CH_2$), 24.7 ($CH_3$), 24.9 ($CH_3$), 30.1 ($CH_2$), 31.2 ($CH_2$), 32.7 ($CH_2$), 35.7 ($CH_2$), 36.7 (t, $J$ = 24.9 Hz, $CH_2$), 36.8 (t, $J$ = 25.9 Hz, $CH_2$), 37.7 (*C*H), 38.7 (*C*H), 82.9 (*C*), 125.68 (t, $J$ = 234.3 Hz, $CF_2$), 125.72 (*C*H), 128.28 (*C*H), 128.32 (*C*H), 142.2 (*C*). $^{19}$F NMR (373 MHz, $CDCl_3$): δ –97.6 to –95.1 (m, 2F). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{24}H_{37}O_2{}^{11}BF_2Na$, 429.2751; found, 429.2746.

**2-{[2-(2,2-Difluorodecyl)cyclopentyl]methyl}-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (7b).**



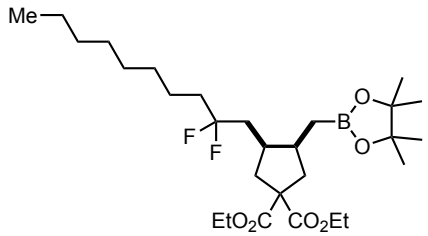

**7b**

Prepared according to procedure **A** described above, except the catalyst loading {10 mol% of $[Cu(MeCN)_4]BF_4$ and 15 mol% of IMes•HCl was used.}. The reaction was conducted for 2 h with 48.6 mg (0.20 mmol) of **1f** and 108.4 μL (0.80 mmol) of **2r**. The product **7b** was obtained in 67% yield (51.9 mg) with *cis*:*trans* = 83:17, which was determined by GC-analysis of the crude reaction mixture.

$^1$H NMR (396 MHz, $CDCl_3$): δ 0.52–0.81 (m, 2H), 0.88 (t, $J$ = 7.1 Hz, 3H), 1.08–1.33 (m, 13H), 1.24 (s, 6H), 1.25 (s, 6H), 1.35–1.57 (m, 4H), 1.60–2.21 (m, 7H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 11.5 (br, B–$CH_2$), 22.3 ($CH_2$), 22.4 (t, $J$ = 4.8 Hz, $CH_2$), 22.6 ($CH_2$), 24.7 ($CH_3$), 24.9 ($CH_3$), 29.1 ($CH_2$),

29.3 ($CH_2$), 29.4 ($CH_2$), 30.1 ($CH_2$), 31.8 ($CH_2$), 32.7 ($CH_2$), 36.6 (t, $J$ = 24.5 Hz, $CH_2$), 37.0 (t, $J$ = 25.4 Hz, $CH_2$), 37.7 (*C*H), 38.7 (*C*H), 82.9 (*C*), 125.9 (t, $J$ = 241.9 Hz, $CF_2$). $^{19}$F NMR (373 MHz, $CDCl_3$): δ –97.4 to –94.6 (m, 2F). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{22}H_{41}O_2BF_2Na$, 409.3064; found, 409.3060.

**Diethyl 3-(2,2-difluorodecyl)-4-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]cyclopentane-1,1-dicarboxylate (7c).**

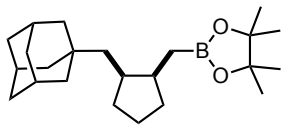



**7c**

Prepared according to procedure **A** described above, except the catalyst loading {10 mol% of $[Cu(MeCN)_4]BF_4$ and 15 mol% of IMes•HCl was used.}. The reaction was conducted for 2 h with 49.3 mg (0.20 mmol) of **1f** and 193.4 μL (0.80 mmol) of **2s**. The product **7c** was obtained in 59% yield (63.6 mg) with *cis*:*trans* = 91:9, which was determined by GC-analysis of the crude reaction mixture.

$^1$H NMR (401 MHz, $CDCl_3$): δ 0.60–0.80 (m, 2H), 0.88 (t, $J$ = 6.6 Hz, 3H), 1.20–1.34 (m, 15H), 1.24 (s, 12H), 1.38–1.50 (m, 2H), 1.61–1.99 (m, 5H), 2.01–2.17 (m, 2H), 2.24–2.36 (m, 2H), 2.43 (ddd, $J$ = 6.2, 13.6, 19.2 Hz, 2H), 4.17 (q, $J$ = 4.7 Hz, 4H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 11.5 (br, B–$CH_2$), 13.97 ($CH_3$), 14.02 ($CH_3$), 22.3 ($CH_2$), 22.6 ($CH_2$), 24.7 ($CH_3$), 24.8 ($CH_3$), 29.1 ($CH_2$), 29.30 ($CH_2$), 29.33 ($CH_2$), 31.8 ($CH_2$), 36.0 (t, $J$ = 24.9 Hz, $CH_2$), 37.031 (*C*H), 37.034 (t, $J$ = 25.9 Hz, $CH_2$), 38.4 (*C*H), 38.6 ($CH_2$), 41.0 ($CH_2$), 58.8 (*C*), 61.3 ($CH_2$), 83.0 (*C*), 125.4 (t, $J$ = 242.4 Hz, $CF_2$), 172.7 (*C*), 172.8 (*C*). $^{19}$F NMR (373 MHz, $CDCl_3$): δ –98.0 to –95.6 (m, 2F). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{28}H_{49}O_6{}^{11}BF_2Na$, 553.3488; found, 553.3486.

**2-[(2-{[(3*r*,5*r*,7*r*)-Adamantan-1-yl]methyl}cyclopentyl)methyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (7d).**

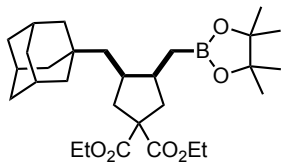


**7d**

Prepared according to procedure **B** described above, except the catalyst loading {10 mol% of $[Cu(MeCN)_4]BF_4$ and 15 mol% of IMes•HCl was used.}. The reaction was conducted for 3 h with 43.0 mg (0.20 mmol) of **1c** and 108.4 μL (0.80 mmol) of **2r**. The product **7d** was obtained in 74% yield (53.2 mg) with *cis*:*trans* = 80:20, which was determined by GC-analysis of the crude reaction mixture.

$^1$H NMR (399 MHz, $CDCl_3$): δ 0.47–0.57 (m, 1H), 0.76–0.92 (m, 2H), 1.19–1.34 (m, 4H), 1.24 (s, 12H), 1.37–1.54 (m, 7H), 1.57–1.72 (m, 8H), 1.77–1.87 (m, 1H), 1.88–1.95 (m, 3H), 1.99–2.13 (m, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 11.2 (br, B–*C*H), 22.3 (*C*$H_2$), 24.7 (*C*$H_3$), 24.9 (*C*$H_3$), 28.8 (*C*H), 32.0 (*C*$H_2$), 32.8 (*C*), 32.9 (*C*$H_2$), 37.2 (*C*$H_2$), 38.0 (*C*H), 39.9 (*C*H), 43.1 (*C*$H_2$), 45.3 (*C*$H_2$), 82.8 (*C*). HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{23}H_{39}O_2{}^{11}B$, 358.3047; found, 358.3044.

**Diethyl 3-{[(3*r*,5*r*,7*r*)-adamantan-1-yl]methyl}-4-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]cyclopentane-1,1-dicarboxylate (7e).**

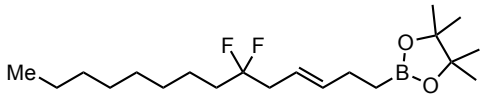


**7e**

Prepared according to procedure **B** described above, except the catalyst loading {10 mol% of $[Cu(MeCN)_4]BF_4$ and 15 mol% of IMes•HCl was used.}. The reaction was conducted for 3 h with 43.0 mg (0.20 mmol) of **1c** and 193.4 μL (0.80 mmol) of **2s**. The product **7e** was obtained in 71% yield (71.7 mg) with *cis*:*trans* = 87:13, which was determined by GC-analysis of the crude reaction mixture.

$^1$H NMR (392 MHz, $CDCl_3$): δ 0.51–0.65 (m, 1H), 0.76–0.98 (m, 2H), 1.17–1.29 (m, 8H), 1.24 (s, 12H), 1.39–1.53 (m, 6H), 1.57–1.72 (m, 6H), 1.88–1.95 (m, 3H), 2.02–2.12 (m, 2H), 2.20 (tt, *J* = 5.5, 10.7 Hz, 1H), 2.35 (ddd, *J* = 6.6, 13.3, 23.6 Hz, 2H), 4.17 (q, *J* = 4.7 Hz, 4H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 11.4 (br, B–*C*H), 14.0 (*C*$H_3$), 24.7 (*C*$H_3$), 24.9 (*C*$H_3$), 28.7 (*C*H), 32.6 (*C*), 37.1 (*C*$H_2$), 37.6 (*C*H), 39.6 (*C*H), 40.4 (*C*$H_2$), 41.1 (*C*$H_2$), 43.0 (*C*$H_2$), 44.3 (*C*$H_2$), 59.0 (*C*), 61.1 (*C*$H_2$), 82.9 (*C*), 172.9 (*C*), 173.3 (*C*). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{29}H_{47}O_6{}^{11}BNa$, 525.3363; found, 525.3356.

**2-(6,6-Difluorotetradec-3-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (8).**



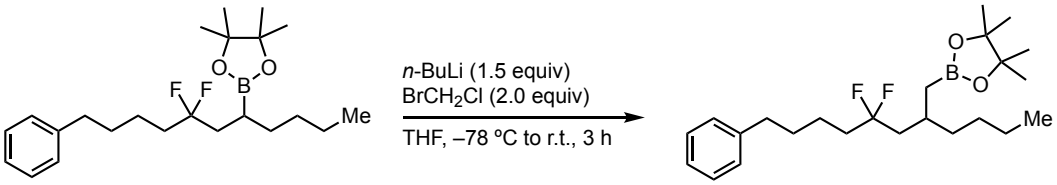

**8**

Prepared according to procedure **A** described above, except the catalyst loading {10 mol% of $[Cu(MeCN)_4]BF_4$ and 15 mol% of IMes•HCl was used.}. The reaction was conducted for 3 h with 49.3 mg (0.20 mmol) of **1f** and 66.8 μL (0.80 mmol) of **2t**. The product **8** was obtained in 63% yield (46.0 mg) with *E*/*Z* = 78/22, which was determined by $^1$H NMR analysis.

$^1$H NMR (396 MHz, $CDCl_3$, *indicates a signal of the minor isomer): δ 0.81–0.94 (m, 5H), 1.20–1.34 (m, 10H), 1.25 (s, 12H), 1.38–1.51 (m, 2H), 1.69–1.87 (m, 2H), 2.15 (q, *J* = 7.3 Hz, 2H), 2.50 (td, *J* = 7.3, 15.4 Hz, 1.56H), *2.61 (td, *J* = 7.1, 15.7 Hz, 0.44H), 5.30 (dtt, *J* = 1.9, 5.7, 13.6 Hz, 1H), 5.57 (dt, *J* = 7.0, 14.4 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$, *indicates signals of the minor isomer): δ 10.6 (br, B–*C*H$_2$), 14.1 (*C*H$_3$), *21.8 (*C*H$_2$), 22.0 (t, *J* = 4.4 Hz, *C*H$_2$), 22.6 (*C*H$_2$), 24.8 (*C*H$_3$), 26.8 (*C*H$_2$), 29.1 (*C*H$_2$), 29.3 (*C*H$_2$), 31.8 (*C*H$_2$), 35.7 (t, *J* = 25.0 Hz, *C*H$_2$), 39.9 (t, *J* = 26.4 Hz, *C*H$_2$), 83.0 (*C*), *119.5 (t, *J* = 5.2 Hz, *C*H), 120.1 (t, *J* = 6.2 Hz, *C*H), 124.7 (t, *J* = 242.4 Hz, *C*F$_2$), *136.2 (*C*H), 137.8 (*C*H). $^{19}$F NMR (373 MHz, $CDCl_3$): δ –97.6 to –97.4 (m, 2F). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{20}H_{37}O_2{}^{11}BF_2Na$, 381.2751; found, 381.2747.

## Derivatization of Akyl Boronates

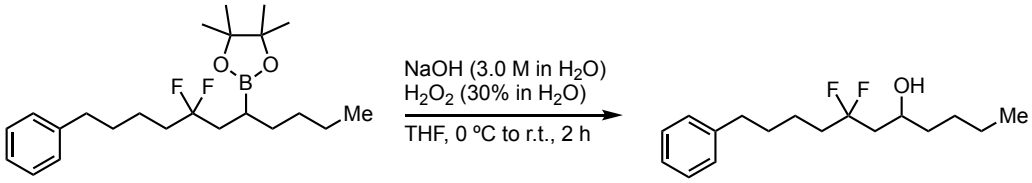
### Experimental Procedure of Homologation of 4aa.




Homologation reaction of **4aa** was performed according to the literature procedure.[13] In an oven-dried reaction vial, **4aa** (40.6 mg, 0.10 mmol) and $BrCH_2Cl$ (13.4 μL, 0.20 mmol) were dissolved in THF (600 μL) in a nitrogen atmosphere and the mixture was cooled to –78 °C. A solution of *n*-BuLi in hexane (1.6 M, 94 μL, 0.15 mmol) was then added dropwise to the reaction mixture, and the mixture was allowed to stir at r.t. for 3 h. 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. After evaporation, the crude material was purified by silica gel chromatography ($Et_2O$/hexane, 0:100–8:92) to give the corresponding boronate **6a** (36.5 mg, 0.089 mmol, 87%) as a colorless oil.

$^1H$ NMR (392 MHz, $CDCl_3$): δ 0.84–0.92 (m, 5H), 1.17–1.32 (m, 7H), 1.23 (s, 12H), 1.47–1.54 (m, 2H), 1.66 (dt, *J* = 7.4, 15.2 Hz, 2H), 1.73–1.95 (m, 4H), 2.63 (t, *J* = 7.6 Hz, 2H), 7.16–7.21 (m, 3H), 7.24–7.31 (m, 2H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 14.1 (*C*$H_3$), 17.4 (br, B–*C*H), 22.0 (t, *J* = 4.8 Hz, *C*$H_2$), 22.9 (*C*$H_2$), 24.80 (*C*$H_3$), 24.84 (*C*$H_3$), 28.8 (*C*$H_2$), 29.1 (*C*H), 31.2 (*C*$H_2$), 35.7 (*C*$H_2$), 36.72 (*C*$H_2$), 36.73 (t, *J* = 25.4 Hz, *C*$H_2$), 42.3 (t, *J* = 24.0 Hz, *C*$H_2$), 82.9 (*C*), 125.7 (*C*H), 125.8 (t, *J* = 245.8 Hz, *C*$F_2$), 128.29 (*C*H), 128.34 (*C*H), 142.2 (*C*). $^{19}F$ NMR (373 MHz, $CDCl_3$): δ –95.1 (t, *J* = 17.2 Hz, 2F). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{24}H_{39}O_2{}^{11}BF_2Na$, 431.2908; found, 431.2906.

**Experimental Procedure of Oxidation of 4aa.**

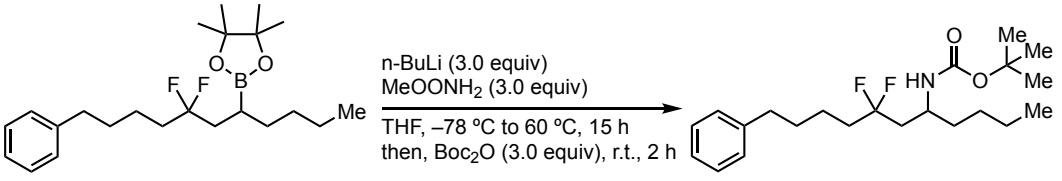



**4aa** **6b**

In a reaction vial, **4aa** (40.4 mg, 0.10 mmol) was dissolved in THF (3 mL), then the reaction mixture was cooled to 0 ºC. 3.0 M $NaOH_{aq}$ and 30% $H_2O_{2aq}$ were subsequently added to the reaction mixture at 0 ºC under air, and then the reaction mixture was allowed to stir at r.t. for 2 h. The reaction mixture was then quenched by addition of a saturated aqueous $Na_2S_2O_3$ solution and extracted three times with $Et_2O$. The combined organic layer was dried over $MgSO_4$ followed by filtration. The crude material was purified by silica gel chromatography (EtOAc/hexane, 0:100–8:92) to give the corresponding alcohol **6b** (25.8 mg, 0.091 mmol, 91%) as a colorless oil.

$^1$H NMR (392 MHz, $CDCl_3$): δ 0.91 (t, $J$ = 7.3 Hz, 3H), 1.23–1.55 (m, 8H), 1.67 (dt, $J$ = 7.6, 15.4 Hz, 2H), 1.84–2.04 (m, 4H), 2.63 (t, $J$ = 7.6 Hz, 2H), 3.96–4.04 (m, 1H), 7.15–7.22 (m, 3H), 7.25–7.31 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 14.0 ($C$H$_3$), 21.9 (t, $J$ = 4.8 Hz, $C$H$_2$), 22.6 ($C$H$_2$), 27.5 ($C$H$_2$), 31.1 ($C$H$_2$), 35.7 ($C$H$_2$), 37.0 (t, $J$ = 25.4 Hz, $C$H$_2$), 37.3 ($C$H$_2$), 43.4 (t, $J$ = 23.5 Hz, $C$H$_2$), 66.8 (t, $J$ = 4.3 Hz, $C$H), 125.4 (t, $J$ = 241.9 Hz, $C$F$_2$), 125.8 ($C$H), 128.32 ($C$H), 128.34 ($C$H), 142.1 ($C$). $^{19}$F NMR (373 MHz, $CDCl_3$): δ –97.6 to –95.6 (m, 2F). HRMS–EI ($m/z$): $[M]^+$ calcd for $C_{17}H_{26}OF_2$, 284.1952; found, 284.1958.

**Experimental Procedure of Amination of 4aa.**

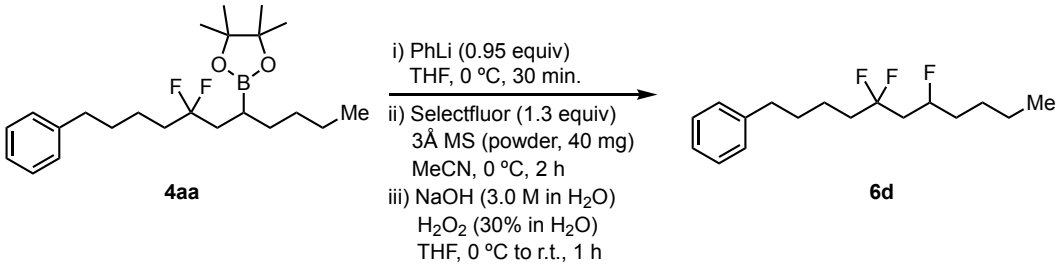



**4aa** **6c**

Amination of **4aa** was performed according to the literature procedure.[14] In an oven-dried reaction vial, $MeONH_2$ (0.77 M in THF, 392 μL, 0.30 mmol) was dissolved in THF (600 μL). After the mixture was cooled to –78 °C, a solution of *n*-BuLi in hexane (1.6 M, 188 μL, 0.30 mmol) was added dropwise under a nitrogen atmosphere. Then **4aa** (40.0 mg, 0.10 mmol) in THF (340 μL) was added dropwise to the solution and stirred at 60 ºC. After 15 h, $(Boc)_2O$ (68.9 μL, 0.30 mmol) was added to the mixture and stirred for 2 h at r.t. The mixture was then quenched by addition of $H_2O$ and extracted three times with EtOAc. The combined organic layer was dried over $MgSO_4$ followed by filtration and evaporation. After purification by flash silica gel column chromatography ($Et_2O$/hexane, 3:97–12:88), **6c** was further purified by GPC to give a pure product (20.5 mg, 0.053 mmol, 53%) as a white solid.

$^1$H NMR (392 MHz, $CDCl_3$): δ 0.89 (t, $J$ = 6.9 Hz, 3H), 1.22–1.37 (m, 4H), 1.43 (s, 9H), 1.46–1.55 (m, 4H), 1.66 (dt, $J$ = 7.7, 15.6 Hz, 2H), 1.81–2.04 (m, 4H), 2.62 (t, $J$ = 7.6 Hz, 2H), 3.70–3.88 (m, 1H), 4.33–4.50 (m, 1H), 7.14–7.21 (m, 3H), 7.24–7.31 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 14.0 ($CH_3$), 21.9 (t, $J$ = 4.3 Hz, $CH_2$), 22.4 ($CH_2$), 27.9 ($CH_2$), 28.4 ($CH_3$), 31.1 ($CH_2$), 35.6 ($CH_2$), 35.7 ($CH_2$), 36.3 (t, $J$ = 25.4 Hz, $CH_2$), 41.2 (t, $J$ = 23.0 Hz, $CH_2$), 46.4 ($CH$), 79.2 ($C$), 124.8 (t, $J$ = 241.5 Hz, $CF_2$), 125.7 ($CH$), 128.3 ($CH$), 128.4 ($CH$), 142.1 ($C$), 155.3 ($C$). $^{19}$F NMR (373 MHz, $CDCl_3$): δ –95.2 to –94.9 (m, 2F). HRMS–ESI ($m/z$): $[M+Na]^+$ calcd for $C_{22}H_{35}O_2NF_2Na$, 406.2528; found, 406.2527.

**Experimental Procedure of Fluorination of 4aa.**

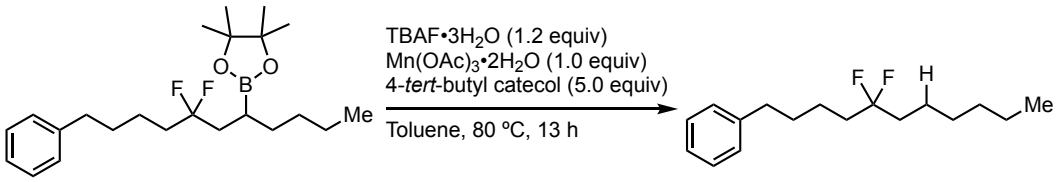



Fluorination of **4aa** was performed according to the literature procedure.[15] In an oven-dried reaction vial, **4aa** (39.5 mg, 0.10 mmol) was dissolved in THF (1 mL). After the mixture was cooled to 0 °C, a solution of PhLi in butyl ether (1.6 M, 59.4 μL, 0.095 mmol) was added dropwise, and the reaction mixture was stirred at 0 ºC for 30 min. After that, MeCN (200 μL) was added to the reaction mixture, and the volatiles were removed *in vacuo* upon warming to r.t. A nitrogen atmosphere was re-established, and MeCN (1 mL) was added. In a separate oven-dried reaction vial, Selectfluor (46.1 mg, 0.13 mmol) and 3Å MS (powder, 40 mg) were dissolved in MeCN (1 mL) at 0 ºC under a nitrogen atmosphere. The pre-prepared solution of **4aa** with PhLi in MeCN was added dropwise to the separate reaction mixture of Selectfluor and 3Å MS in MeCN, and the mixture was stirred at r.t. for 2 h. The mixture was then passed through a short plug of silica gel (Φ: 10 mm, height of the silica-gel column: 30 mm), eluted with $Et_2O$ and volatiles were removed in vacuo. The crude material was purified by silica gel chromatography (hexane only), before the excess boronic ester and PhB(pin) were oxidized by the addition of 3M $NaOH_{aq}$ (500 μL) and 30% $H_2O_{2aq}$ (500 μL) in THF (3 mL). After 1 h, the mixture was extracted three times with $Et_2O$, dried over $MgSO_4$. The resultant mixture was purified again by silica gel chromatography ($Et_2O$/hexane, 0:100–2:98) to give **6d** (17.7 mg, 0.062 mmol, 62%) as colorless oil.

$^1$H NMR (392 MHz, $CDCl_3$): δ 0.92 (t, $J$ = 7.1 Hz, 3H), 1.20–1.47 (m, 4H), 1.49–1.59 (m, 2H),

1.61–1.75 (m, 4H), 1.84–2.32 (m, 4H), 2.63 (t, $J$ = 7.6 Hz, 2H), 4.75 (dtt, $J$ = 3.9, 8.0, 49.5 Hz, 1H), 7.14–7.22 (m, 3H), 7.24–7.31 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 13.9 (*C*H$_3$), 21.9 (t, $J$ = 4.3 Hz, *C*H$_2$), 22.4 (*C*H$_2$), 26.9 (d, $J$ = 4.8 Hz, *C*H$_2$), 31.1 (*C*H$_2$), 35.3 (d, $J$ = 21.1 Hz, *C*H$_2$), 35.7 (*C*H$_2$), 36.6 (dt, $J$ = 1.1, 24.9 Hz, *C*H$_2$), 41.8 (dt, $J$ = 13.0, 25.6 Hz, *C*H$_2$), 89.1 (d, $J$ = 166.7 Hz, *C*H–F), 124.0 (t, $J$ = 242.4 Hz, *C*F$_2$), 125.8 (*C*H), 128.3 (*C*H), 128.4 (*C*H), 142.2 (*C*). $^{19}$F NMR (369 MHz, $CDCl_3$): δ –180.4 to –179.9 (m, 1F), –98.2 to –97.3 (m, 1F), –95.0 to –94.0 (m, 1F). HRMS–EI ($m/z$): $[M]^+$ calcd for $C_{17}H_{25}F_3$, 286.1908; found, 286.1911.

**Experimental Procedure of Protonation of 4aa.**

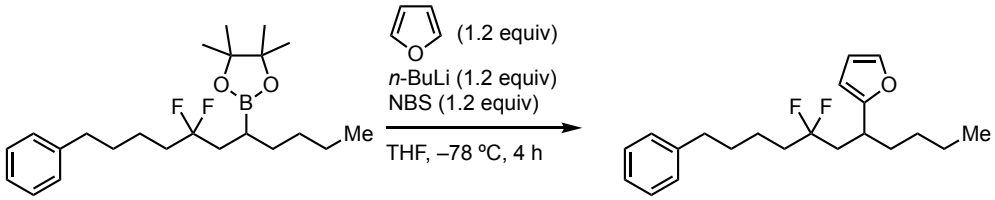



**4aa** **6e**

Protonation of **4aa** was performed according to the literature procedure.[16] In a reaction vial, TBAF•3$H_2O$ (37.9 mg, 0.12 mmol), $Mn(OAc)_3$•2$H_2O$ (26.8 mg, 0.1 mmol), and *tert*-butyl catechol (97.9 mg, 0.59 mmol) were dissolved in toluene (600 μL). Then **4aa** (39.7 mg, 0.10 mmol) in toluene (700 μL) was added dropwise to the mixture under a nitrogen atmosphere and stirred at 80 ºC for 13 h. The mixture was then passed through a short plug of silica gel (Φ: 10 mm, the height of the silica-gel column: 30 mm), eluted with $Et_2O$, and volatiles were removed in vacuo. The crude material was purified by silica gel chromatography ($Et_2O$/hexane, 0:100–2:98) to give **6e** (15.0 mg, 0.056 mmol, 56%) as a colorless oil.

$^1$H NMR (392 MHz, $CDCl_3$): δ 0.89 (t, *J* = 6.7 Hz, 3H), 1.21–1.36 (m, 6H), 1.38–1.477 (m, 2H), 1.480–1.54 (m, 2H), 1.61–1.90 (m, 6H), 2.63 (t, *J* = 8.0 Hz, 2H), 7.15–7.21 (m, 3H), 7.24–7.31 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 14.0 (*C*$H_3$), 22.0 (t, *J* = 4.8 Hz, *C*$H_2$), 22.3 (t, *J* = 4.8 Hz, *C*$H_2$), 22.5 (*C*$H_2$), 29.1 (*C*$H_2$), 31.2 (*C*$H_2$), 31.6 (*C*$H_2$), 35.7 (*C*$H_2$), 36.1 (t, *J* = 25.4 Hz, *C*$H_2$), 36.3 (t, *J* = 25.4 Hz, *C*$H_2$), 125.3 (t, *J* = 241.0 Hz, *C*$F_2$), 125.8 (*C*H), 128.3 (*C*H), 128.4 (*C*H), 142.2 (*C*). $^{19}$F NMR (369 MHz, $CDCl_3$): δ –98.1 (t, *J* = 16.9 Hz, 2F). HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{17}H_{26}F_2$, 268.2003; found, 268.2004.

**Experimental Procedure of Arylation of 4aa.**

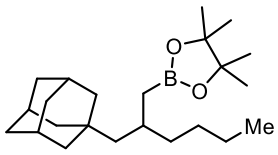



**4aa** **6f**

Arylation of **4aa** was performed according to the literature procedure.[17] To an oven-dried reaction vial, furan (10.0 μL, 0.13 mmol) in THF (400 μL) was added, and the mixture was cooled to –78 ºC under a nitrogen atmosphere. A solution of *n*-BuLi in hexane (1.6 M, 75 μL, 0.12 mmol) was then added dropwise and stirred at r.t. for 30 min. After that, **4aa** (39.4 mg, 0.1 mmol) in THF (200 μL) was added dropwise to the mixture at –78 ºC and stirred for 1 h, then the NBS (21.4 mg, 0.12 mmol) in THF (400 μL) was added to this reaction mixture. After the reaction mixture was stirred at –78 ºC for 2 h, the mixture was quenched by addition of $Na_2S_2O_3$ and extracted three times with $Et_2O$. The combined organic layer was dried over $MgSO_4$ followed by filtration. After evaporation, the remained crude material was purified by silica gel chromatography ($Et_2O$/hexane, 0:100–6:94) to give **6f** (21.6 mg, 0.065 mmol, 65%) as a colorless oil.

$^1$H NMR (392 MHz, $CDCl_3$): δ 0.85 (t, $J$ = 7.5 Hz, 3H), 1.08–1.46 (m, 6H), 1.58–1.76 (m, 6H), 1.98–2.13 (m, 1H), 2.17–2.34 (m, 1H), 2.56 (t, $J$ = 7.6 Hz, 2H), 2.92–3.02 (m, 1H), 6.00 (d, $J$ = 3.1 Hz, 1H), 6.27 (dd, $J$ = 1.3, 2.7 Hz, 1H), 7.10–7.21 (m, 3H), 7.23–7.32 (m, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 13.9 ($CH_3$), 21.9 (t, $J$ = 4.8 Hz, $CH_2$), 22.4 ($CH_2$), 29.2 ($CH_2$), 31.2 ($CH_2$), 33.4 (t, $J$ = 3.8 Hz, *C*H), 34.8 ($CH_2$), 35.7 ($CH_2$), 36.3 (t, $J$ = 25.4 Hz, $CH_2$), 40.4 (t, $J$ = 25.4 Hz, $CH_2$), 105.4 (*C*H), 110.0 (*C*H), 124.8 (t, $J$ = 242.4 Hz, $CF_2$), 125.7 (*C*H), 128.29 (*C*H), 128.34 (*C*H), 140.8 (*C*H), 142.2 (*C*), 157.4 (*C*). $^{19}$F NMR (369 MHz, $CDCl_3$): δ –98.4 to –97.4 (m, 1F), –95.0 to –94.1 (m, 1F). HRMS–EI ($m/z$): $[M]^+$ calcd for $C_{21}H_{28}OF_2$, 334.2108; found, 334.2107.

**2-(2-(((3r,5r,7r)-adamantan-1-yl)methyl)hexyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6g).**

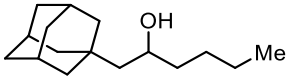



**6g**

Prepared according to the described procedure as for the boronate **6a**. The reaction was conducted for 3 h with 36.8 mg (0.11 mmol) of **4ca**. The product **6g** was obtained in 87% yield (33.3 mg, 0.087 mmol).

$^{1}$H NMR (392 MHz, $CDCl_3$): δ 0.79 (t, *J* = 6.3 Hz, 2H), 0.88 (t, *J* = 6.9 Hz, 3H), 0.93–1.00 (m, 1H), 1.05–1.13 (m, 1H), 1.16 –1.37 (m, 6H), 1.24 (s, 12H), 1.45–1.53 (m, 6H), 1.58–1.73 (m, 7H), 1.88–1.97 (m, 3H). $^{13}$C NMR (99 MHz, $CDCl_3$): δ 14.2 (*C*$H_3$), 20.1 (br, B–*C*$H_2$), 23.1 (*C*$H_2$), 24.8 (*C*$H_3$), 24.9 (*C*$H_3$), 28.5 (*C*H), 28.8 (*C*H), 29.3 (*C*$H_2$), 33.1 (*C*), 37.2 (*C*$H_2$), 38.8 (*C*$H_2$), 43.1 (*C*$H_2$), 52.3 (*C*$H_2$), 82.7 (*C*). HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{23}H_{42}{}^{11}BO_2$, 361.3277; found, 361.3272.

**1-((3r,5r,7r)-adamantan-1-yl)hexan-2-ol (6h).**

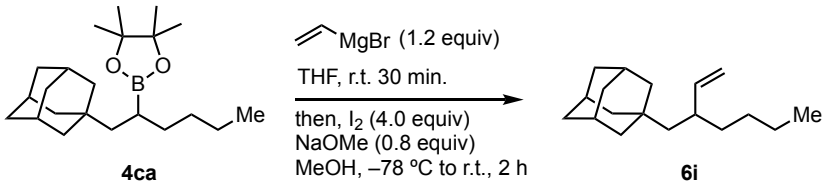



**6h**

Prepared according to the described procedure as for the alcohol **6b**. The reaction was conducted for 3 h with 36.5 mg (0.11 mmol) of **4ca**. The product **6h** was obtained in 92% yield (22.8 mg, 0.096 mmol).

$^{1}$H NMR (401 MHz, $CDCl_3$): δ 0.91 (t, *J* = 7.0 Hz, 3H), 1.11–1.50 (m, 12H), 1.52–1.58 (m, 2H), 1.66 (t, *J* = 13.8 Hz, 3H), 1.69 (t, *J* = 13.8 Hz, 3H), 1.91–1.99 (m, 3H), 3.76–3.85 (m, 1H). $^{13}$C NMR (99 MHz, $CDCl_3$): δ 14.1 (*C*$H_3$), 22.7 (*C*$H_2$), 27.8 (*C*$H_2$), 28.7 (*C*H), 32.2 (*C*), 37.1 (*C*$H_2$), 39.3 (*C*$H_2$), 43.1 (*C*$H_2$), 52.5 (*C*$H_2$), 68.0 (*C*H). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{16}H_{28}ONa$, 259.2038; found, 259.2032.

**Experimental Procedure of Olefination of 4ca.**

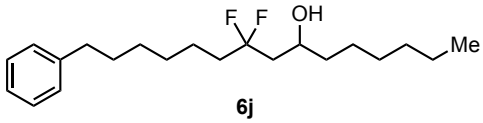



**4ca** **6i**

To an oven-dried reaction vial, **4ca** (36.4 mg, 0.1 mmol) in THF (1 mL) was added, then vinyl magnesium bromide (1.0 M in THF, 400 μL, 0.4 mmol) was added to the reaction mixture at r.t. under a nitrogen atmosphere. The reaction mixture was stirred at r.t. for 30 min., then cooled to –78 ºC. A solution of $I_2$ (50.8 mg, 0.4 mmol) in MeOH (1.3 mL) was added dropwise to the reaction mixture and stirred for another 30 min. After that, NaOMe (43.2 mg, 0.8 mmol) in MeOH (1.6 mL) was added dropwise to the mixture. The mixture was warmed up to r.t. and stirred for 2 h. The mixture was then quenched by addition of $Na_2S_2O_3$ and extracted three times with $Et_2O$. The combined organic layer was dried over $MgSO_4$ followed by filtration. The crude material was purified by silica gel chromatography ($Et_2O$/hexane, 0:100–4:96) to give **6i** (17.5 mg, 0.066 mmol, 66%) as a colorless oil.

$^1$H NMR (392 MHz, $CDCl_3$): δ 0.87 (t, $J$ = 7.1 Hz, 3H), 1.04–1.15 (m, 2H), 1.17–1.32 (m, 6H), 1.41–1.53 (m, 6H), 1.62 (t, $J$ = 14.4 Hz, 3H), 1.66 (t, $J$ = 14.6 Hz, 3H), 1.87–1.95 (m, 3H), 2.06–2.18 (m, 1H), 4.85–4.94 (m, 2H), 5.52–5.64 (m, 1H). $^{13}$C NMR (99 MHz, $CDCl_3$): δ 14.1 ($C$H$_3$), 22.8 ($C$H$_2$), 28.8 ($C$H), 29.3 ($C$H$_2$), 33.2 ($C$), 37.2 ($C$H$_2$), 37.4 ($C$H$_2$), 38.7 ($C$H), 43.1 ($C$H$_2$), 50.1 ($C$H$_2$), 112.6 ($C$H$_2$), 146.1 ($C$H). HRMS–EI ($m/z$): $[M]^+$ calcd for $C_{18}H_{30}$, 246.2348; found, 246.2352.

**9,9-difluoro-15-phenylpentadecan-7-ol (6j).**

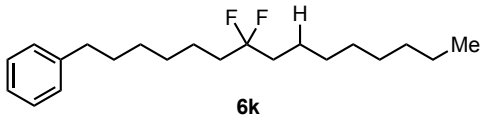



**6j**

Prepared according to the described procedure as for the alcohol **6b**. The reaction was conducted for 3 h with 45.2 mg (0.10 mmol) of **4ub**. The product **6j** was obtained in 87% yield (29.6 mg, 0.087 mmol).

$^{1}$H NMR (392 MHz, $CDCl_3$): δ 0.88 (t, $J$ = 6.5 Hz, 3H), 1.21–1.52 (m, 16H), 1.59–1.67 (m, 2H), 1.79–2.03 (m, 4H), 2.60 (t, $J$ = 7.6 Hz, 2H), 3.97–4.04 (m, 1H), 7.14–7.20 (m, 3H), 7.24–7.31 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 14.0 ($CH_3$), 22.2 (t, $J$ = 4.8 Hz, $CH_2$), 22.6 ($CH_2$), 25.3 ($CH_2$), 29.0 ($CH_2$), 29.16 ($CH_2$), 29.18 ($CH_2$), 31.3 ($CH_2$), 31.8 ($CH_2$), 35.9 ($CH_2$), 37.2 (t, $J$ = 25.4 Hz, $CH_2$), 37.6 ($CH_2$), 43.4 (t, $J$ = 24.0 Hz, $CH_2$), 66.8 ($CH$), 125.5 (t, $J$ = 241.5 Hz, $CF_2$), 125.6 ($CH$), 128.2 ($CH$), 128.4 ($CH$), 142.6 ($C$). $^{19}$F NMR (373 MHz, $CDCl_3$): δ –97.6 to –95.7 (m, 2F). HRMS–EI ($m/z$): $[M]^+$ calcd for $C_{21}H_{34}OF_2$, 340.2578; found, 340.2568.

**(7,7-difluoropentadecyl)benzene (6k).**




**6k**

Prepared according to the described procedure as for **6e**. The reaction was conducted for 18 h with 45.0 mg (0.10 mmol) of **4ub**. The product **6k** was obtained in 53% yield (17.1 mg, 0.053 mmol).

$^{1}$H NMR (401 MHz, $CDCl_3$): δ 0.88 (t, $J$ = 7.0 Hz, 3H), 1.19–1.32 (m, 10H), 1.33–1.38 (m, 4H), 1.40–1.50 (m, 4H), 1.59–1.68 (m, 2H), 1.70–1.85 (m, 4H), 2.60 (t, $J$ = 7.8 Hz, 2H) 7.15–7.21 (m, 3H), 7.24–7.31 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 14.1 ($CH_3$), 22.28 (t, $J$ = 5.8 Hz, $CH_2$), 22.34 (t, $J$ = 5.8 Hz, $CH_2$), 22.6 ($CH_2$), 29.0 ($CH_2$), 29.1 ($CH_2$), 29.3 ($CH_2$), 29.36 ($CH_2$), 29.42 ($CH_2$), 31.3 ($CH_2$), 31.8 ($CH_2$), 35.9 ($CH_2$), 36.26 (t, $J$ = 25.9 Hz, $CH_2$), 36.31 (t, $J$ = 25.4 Hz, $CH_2$), 125.4 (t, $J$ = 241.4 Hz, $CF_2$), 125.6 ($CH$), 128.2 ($CH$), 128.4 ($CH$), 142.7 ($C$). $^{19}$F NMR (373 MHz, $CDCl_3$): δ –98.2 to –98.0 (m, 2F). HRMS–EI ($m/z$): $[M]^+$ calcd for $C_{21}H_{34}F_2$, 324.2629; found, 324.2623.

## Single Crystal X-ray Structural Analysis

The relative stereochemistry of the product **4am** was determined based on X-ray crystallographic analysis. The details were summarized in Figure S1 and Table S1.

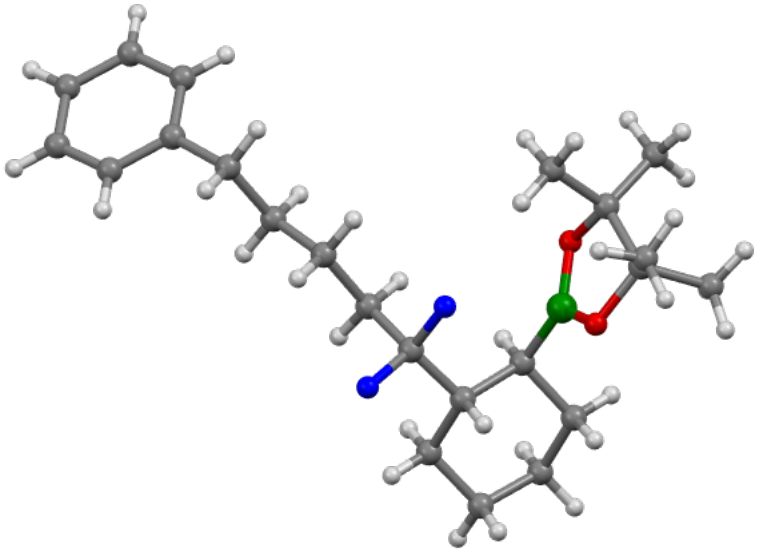


**Figure S1.** Molecular structure of **4am**. Thermal ellipsoids set at 50% probability.

**Table S3.** Summary of X-ray crystallographic data for **4am.**

| | |
|---|---|
| CCDC | 2046556 |
| Empirical formula | $C_{23}H_{35}BF_2O_2$ |
| Formula weight | 392.32 |
| Temperature/K | 123 |
| Crystal system | monoclinic |
| Space group | $P2_1/n$ |
| $a$ / Å | 12.5781(6) |
| $b$ / Å | 10.5058(4) |
| $c$ / Å | 17.3733(9) |
| $\alpha$/° | 90 |
| $\beta$/° | 103.258(5) |
| $\gamma$/° | 90 |
| Volume/Å$^3$ | 2234.57(18) |
| $Z$ | 4 |
| $\rho_{calc}$ g/cm$^3$ | 1.166 |
| $\mu$/mm$^{-1}$ | 0.699 |
| F(000) | 848.0 |
| Crystal size/mm$^3$ | 0.27×0.1×0.07 |
| Radiation | CuKα ($\lambda$ = 1.54184) |
| 2$\theta$ range for data collection/° | 7.884 to 151.834 |
| Index ranges | –15≦$h$≦14, –8≦$k$≦12, –19≦$l$≦21 |
| Reflections collected | 12277 |
| Independent reflections | 4454 [$R_{int}$ = 0.0305, $R_{sigma}$ = 0.0348] |
| Data/restraints/parameters | 4454/0/245 |
| Goodness-of-fit on F$^2$ | 1.044 |
| Final $R$ indexes [I>=2σ (I)] | $R_1$ = 0.0626, $wR_2$ = 0.1733 |
| Final $R$ indexes [all data] | $R_1$ = 0.0774, $wR_2$ = 0.1888 |
| Largest diff. peak/hole / e Å$^{-3}$ | 0.41/–0.32 |

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## List of Publication

*Chapter 1*

Catalytic Enantioselective Synthesis of Allylic Boronates Bearing a Trisubstituted Alkenyl Fluoride and Related Derivatives
Akiyama, S.; Kubota, K.; Mikus, M. S.; Paioti, P. H. S.; Romiti, F.; Liu, Q.; Zhou, Y.; Hoveyda, A. H.; Ito, H.
*Angew. Chem., Int. Ed.* **2019**, *58*, 11998–12003.

*Chapter 2*

Copper(I)-Catalyzed Boryl Substitution of 1-Trifluoromethyl Allenes for the Synthesis of 3-Boryl-Substituted 1,1-*Gem*-Difluorodienes.
Akiyama, S.; Nomura, S.; Kubota, K.; Ito, H.
*J. Org. Chem.* **2020**, 85, 4172–4181.

*Chapter 3*

Dearomatization/Enantioselective Borylation Sequence for the Synthesis of Fluorine-Containing *N*-heterocyclic Boronates
Akiyama, S.; Nomura, S.; Kubota, K.; Ito, H.
*To be submitted*

*Chapter 4*

A Copper(I)-Catalyzed Radical Relay Reaction Enabling the Intermolecular 1,2-Alkylborylation of Unactivated Olefins
Akiyama, S.; Oyama, N.; Endo, T.; Kubota, K.; Ito, H.
*Submitted*

## Other Publications

1. 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.
   *Angew. Chem., Int. Ed.* **2018**, *57*, 7196–7199.
2. Copper(I)-Catalyzed Stereo- and Chemoselective Borylative Radical Cyclization of Alkyl Halides Bearing an Alkene Moiety.
   Iwamoto, H.; Akiyama, S.; Hayama, K.; Ito, H.
   *Org. Lett.* **2017**, *19*, 2614–2617.

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