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RESEARCH ARTICLE

Cu(I)-Catalyzed Enantioselective γ-Boryl Substitution of Trifluoromethyl- and Silyl-substituted Alkenes

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Abstract: Asymmetric γ-boryl substitution of trifluoromethyl- and silyl-substituted alkenes has been investigated. A variety of substrates were reacted with bis(pinacolato)diboron in the presence of a copper(I) salt and optically active C_1 symmetric QuinoxP*-type bisphosphine ligand as the catalyst. The optically active silyl-substituted *gem*-difluoroallylboronates products bearing a stereogenic C–B bond, which have never been synthesized before, were obtained in good yield with high enantioselectivity (up to 83% and up to 86% ee, respectively). The resulting allylboron compounds undergo a stereoselective allylboration with a range of aldehydes to afford chiral silyl- and difluoromethylene-containing homoallylic alcohols without significant loss in their enantiomeric purity. The resulting silyl groups in the derivatives can serve as cross-coupling sites, allowing further transformation into structurally complex fluorinated chiral molecules.

Introduction

Fluorine-containing compounds are important in agricultural and pharmaceutical chemistry.[1] Structural motifs containing fluorine atoms have been used as bioisosteres corresponding to carbonyl and amide moieties to improve the metabolic stability and membrane permeability of several drug candidates.[2] As typical examples of these structural motifs, *gem*-difluoroalkenes and *gem*-difluoromethylene are particularly important and observed in bioactive compounds, such as anti-herpes compounds and Tafluprost (Figure 1A). These compounds contain stereocenters, which make their synthesis more difficult. Because there are only a limited number of examples of the synthesis of compounds containing *gem*-difluoroalkene/methylene moieties bearing stereocenters,[3] the development of new enantioselective synthetic routes to prepare chiral fluorinated molecules is highly desirable to satisfy the requirements of the pharmaceutical industry.

Both allylboronates and allylsilanes have been recognized as versatile building blocks for several decades due to their high synthetic utility in organic chemistry.[4,5] Similarly, 1-silyl-allylboronates have been reported as novel functionalized allylation reagents in several studies (Figure 1B).[6] Following these studies, several methods have been developed to synthesize allylic compounds containing fluorine atoms. Crimmin, Shi, Ogoshi Tellier, and Feng have reported the synthesis of racemic *gem*-difluoroallylsilanes.[7] More recently, Shi and Hoveyda independently reported the synthesis of optically active *gem*-difluoroallylsilanes in 2019.[8] For allylboronates, Hoveyda first reported the synthesis of racemic *gem*-difluoroallylboronates using an *N*-heterocyclic carbene (NHC)/copper(I) complex catalyst in 2011. Jingping, Wang, Cao, Lin, Xu, and Santos have independently reported the preparation of racemic *gem*-difluoroallylboronates.[9]

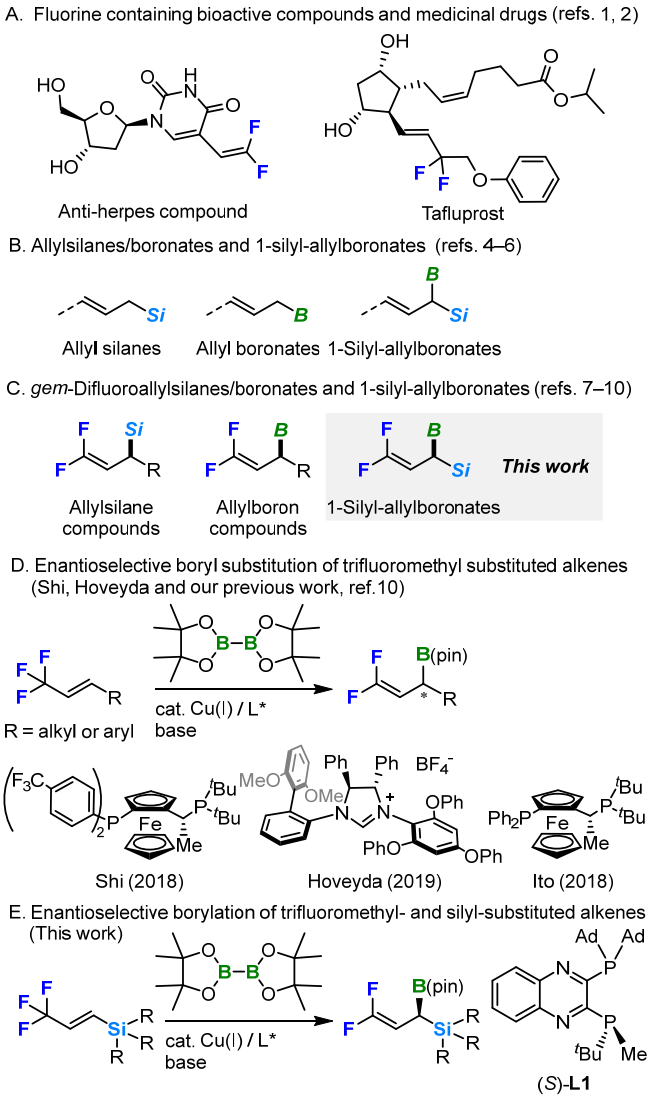


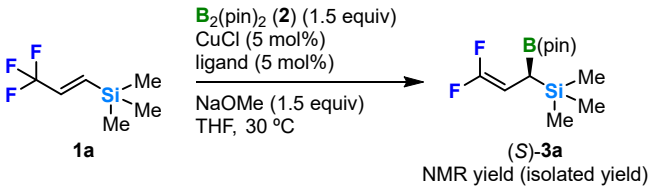
Figure 1. Introduction and background of allylic organoboron and silicon compounds and examples of their synthesis.

Recently, Shi, Hoveyda, and our group reported the use of copper(I)-catalyzed borylation reactions for the enantioselective synthesis of *gem*-difluoroallylboronates (Figure 1C and 1D).[10] However, the enantioselective synthesis of 3,3-difluoro-1-silyl-allylboronates has not been previously reported to the best of our knowledge (Figure 1C and 1E). In this paper, we report the development of a copper(I)-catalyzed enantioselective γ-boryl substitution of trifluoromethyl- and silyl-substituted alkenes used to prepare enantioenriched *gem*-difluoro-1-silyl-allylboronates. Subsequently, the resulting allylboronate products were subjected to several transformations that afford potentially useful chiral fluorinated molecules. In addition, we determined the absolute configuration of the obtained allylboronates using single-crystal X-ray diffraction analysis of the products derived from the initial allylboronate products.

Results and Discussion

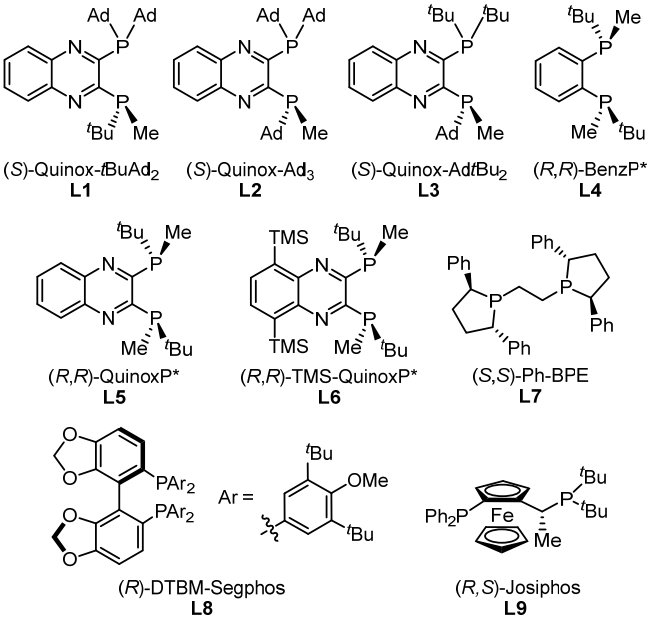
The results of our extensive optimization experiments are shown in Table 1. We found that the reaction conducted using (*E*)-trimethyl(3,3,3-trifluoro-1-propenyl)silane (**1a**) and bis(pinacolato)diboron (**2**) (2.0 equiv) in the presence of CuCl (5 mol%), (*S*)-Quinox-*t*BuAd$_2$ (**L1**) (5 mol%), and NaOMe (1.5 equiv) in THF at 0 to 30 °C afforded (*S*)-**3a** in good yield with high enantioselectivity [83% ^{19}F NMR yield, 86% ee (Table 1, entry 1)].[11,12] On the other hand, (*S*)-Quinox-Ad$_3$ (**L2**), in which the *t*Bu group on the chiral phosphorus atom in **L1** was replaced by a bulkier adamantyl group, gave (*S*)-**3a** with slightly diminished enantioselectivity (70% ^{19}F-NMR yield, 84% ee, entry 2).[11] Moreover, a decreased enantioselectivity was observed when using (*S*)-Quinox-Ad*t*Bu$_2$ (**L3**), which is a less bulky ligand when compared to (*S*)-**L1** (70% ^{19}F-NMR yield, 74% ee, entry 3).[11] (*R,R*)-BenzP* (**L4**), (*R,R*)-QuinoxP* (**L5**), and (*R,R*)-TMS-QuinoxP* (**L6**) were also tested, but product (*S*)-**3a** was obtained with lower enantioselectivity (entries 4–6, 31–96% ^{19}F-NMR yield, –76– –48% ee).[13] (*S,S*)-Ph-BPE (**L7**) and (*R*)-DTBM-Segphos (**L8**), which are C_2 symmetric chiral ligands, gave the desired product (*S*)-**3a** in excellent yield, while only low to moderate enantioselectivities were observed (entries 7 and 8, 93 and 96% ^{19}F-NMR yield, –76 and 8% ee). Finally, we tested the Josiphos-type ligand, (*R,S*)-Josiphos (**L9**), which was identified in our previous study as the best ligand.[9b] However, **L9** was not suitable in this system and gave poor results (entry 9, 96% ^{19}F-NMR yield, –18% ee).

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

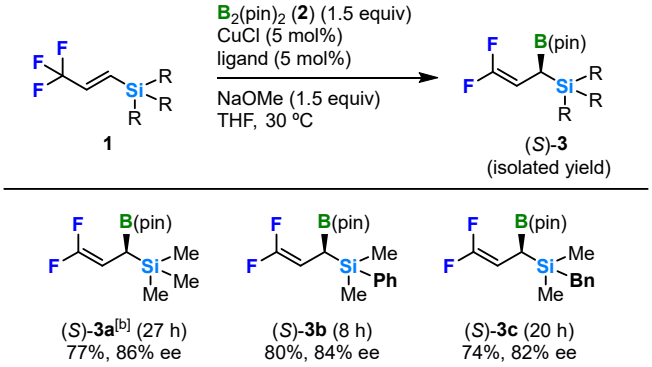


Entry	Ligand	Time (h)	NMR yield (%)[b] (isolated)	% ee
1	**L1**	27	83 (77)	86[c,d]
2	**L2**	6	70 (43)	84[c]
3	**L3**	5	70 (34)	74[c]
4	**L4**	2	93 (68)	–76
5	**L5**	2	31 (23)	–72
6	**L6**	2	96 (73)	–48
7	**L7**	2	93 (73)	8
8	**L8**	2	96 (66)	–76
9	**L9**	2	96 (68)	–18

[a] Reaction conditions: **1a** (0.25 mmol), **2** (0.38 mmol), CuCl, chiral ligand (0.013 mmol), and base (0.375 mmol) in THF (0.5 M). [b] Determined using ^{19}F NMR analysis of the crude product with fluorobenzene used as an internal standard. Isolated yields are shown in the parentheses. Determined using high-performance liquid chromatography (HPLC) analysis after oxidation and acylation. [c] Determined using HPLC after allylboration. [d] **1a** was added at 0 °C and the reaction mixture was heated to 30 °C.

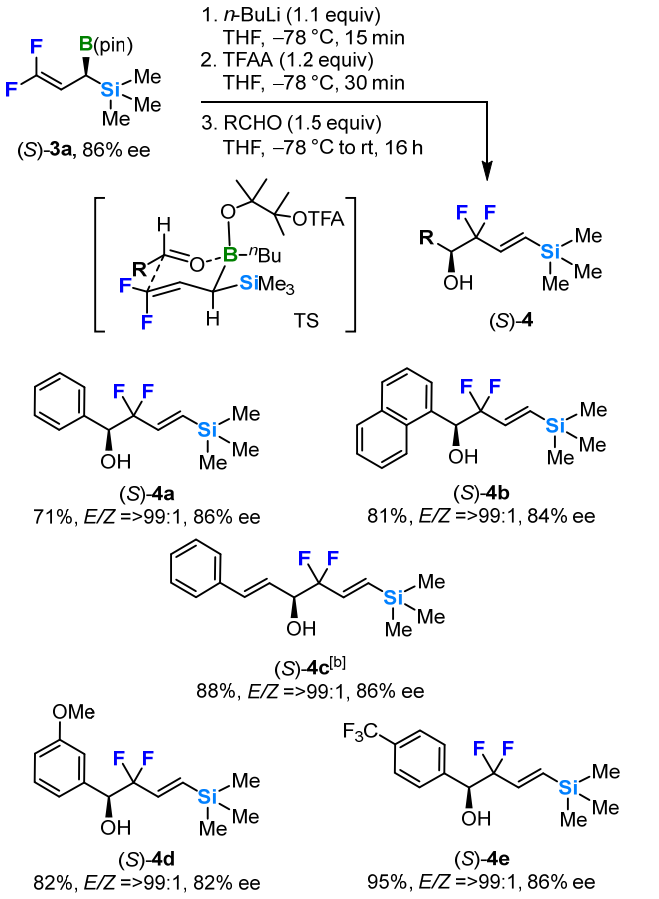


Encouraged by the results shown in Table 1, we attempted to further improve the enantioselectivity using substrates bearing a bulkier substituent on the silicon atom (Scheme 1). Unfortunately, both substrates bearing a dimethylphenyl silyl group (**1b**) and dimethylbenzyl silyl group (**1c**) gave their corresponding allylboronate products [(*S*)-**3b** and (*S*)-**3c**] with lower ee values (84 and 82% ee, respectively) when compared to that of the product bearing a trimethylsilyl group [(*S*)-**3a**].



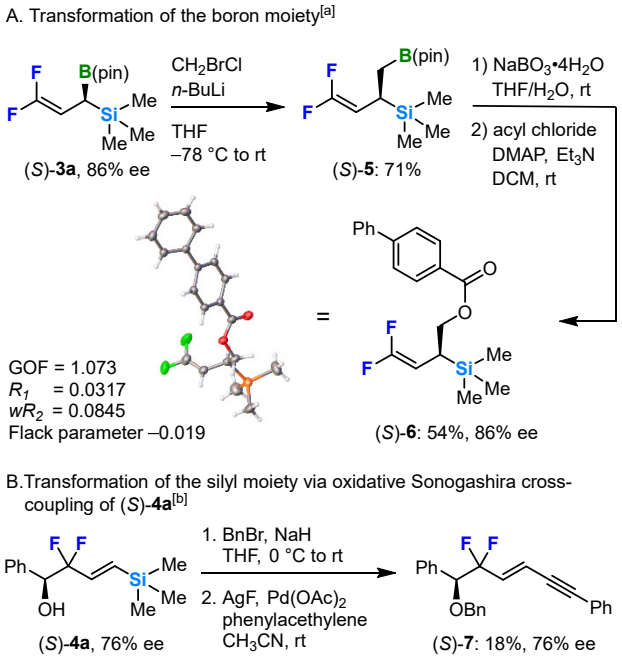
Scheme 1. The effect of the silyl group.[a] [a] The reaction was performed on a 0.25 mmol scale. The ee values were determined using HPLC analysis after allylboration. Isolated yields are shown. [b] 1a was added at 0 °C and the reaction mixture was heated to 30 °C.

We next investigated the utility of this method for the synthesis of a variety of fluorinated compounds with more complicated structures (Scheme 2). The stereoselective allylboration of a variety of aldehydes with (*S*)-**3a** was conducted using the Aggarwal method.[14] We obtained their corresponding homoallylic alcohols with high diastereoselectivity and stereospecificity (up to 95% yield, *E*/*Z* = >99:1, 100% es, Scheme 2). Benzaldehyde, naphthaldehyde, and cinnamaldehyde were successfully applied in the allylation reaction (**4a**–**4c**, 71–88% yield, *E*/*Z* = >99:1, 84–86% ee, 98–100% es). Moreover, aromatic aldehydes bearing electron-donating or electron-withdrawing substituents on the aryl group reacted efficiently with excellent stereospecificity (**4d** and **4e**, 82 and 95% yield, *E*/*Z* = >99:1, 82 and 86% ee, 95 and 100% es, respectively).



Scheme 2. Scope of the allylboration reaction using (*S*)-**3a**.[a] [a] The reaction was performed on a 0.07 mmol scale. The ee values were determined using HPLC analysis. Isolated yields are shown. [b] The reaction was carried out using 1.2 equiv of aldehyde.

The silyl-substituted *gem*-difluoroalkenes synthesized using the copper(I)-catalyzed reaction were subsequently applied in a variety of transformations (Scheme 3A). Fluorinated allylboronate [(*S*)-**3a**] was subjected to a homologation reaction using a halomethyl lithium reagent to produce the desired product [(*S*)-**5**] in good yield (71%).[15] Subsequent oxidation of the boron moiety and acylation were conducted to give the acylated product [(*S*)-**6**] in moderate yield (54%) without any erosion of the enantiomeric purity (86% ee, 100% es). Single-crystal X-ray diffraction analysis of compound **6** was conducted to confirm the structure of the newly synthesized allylboronate [(*S*)-**3a**]. The newly formed stereocenter in **6** has an *S*-configuration. We also performed an oxidative Sonogashira cross-coupling reaction of (*S*)-**4a** (Scheme 3B).[16,17] This reaction allowed the synthesis of chiral 1,3-enynes bearing a *gem*-difluoromethylene moiety [(*S*)-**7**] (25% ^{19}F NMR yield, 18% isolated yield, 76% ee, 100% es).



Scheme 3. Transformations of the allylboronate product. [a] The homologation reaction was performed on a 0.14 mmol scale. The oxidation and acylation reactions were performed on a 0.068 mmol scale. The ee value was determined using HPLC analysis. [b] The benzyl protection reaction was performed on a 0.512 mmol scale. The cross-coupling reaction was conducted on a 0.21 mmol scale. The ee value was determined using HPLC analysis. Deposition Number 2157922 [for (*S*)-**6**] contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

A plausible catalytic cycle for the enantioselective borylation of trifluoromethyl- and silyl-substituted alkenes is shown in Figure 2. Initially, copper(I) alkoxide complex **I**, bearing the bisphosphine ligand, is formed in situ and then reacts with diboron to form borylcopper(I) intermediate **II**. Alkene **1a** coordinates to intermediate **II** to form complex **III**. The regioselectivity and enantioselectivity are determined in the transition state formed between the coordination and insertion steps, in which the electron-withdrawing CF_3 group stabilizes the Cu–C bond. A subsequent borylcupration step affords intermediate **IV**.[10b] The desired product (*S*)-**3a** was obtained via a rapid β-fluoroelimination step. Finally, a metathesis reaction between copper(I) complex **V** and NaOMe regenerated copper(I) alkoxide complex **I**.

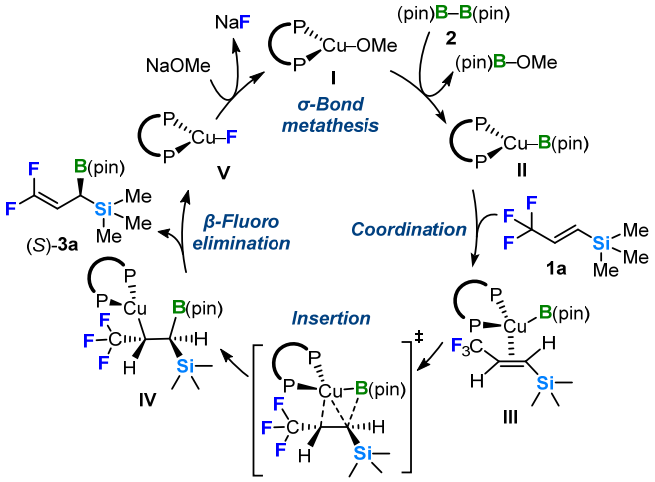


Figure 2. Proposed catalytic cycle.

The proposed transition states (TSs) for the enantio-determining step are shown in Figure 3. The proposed interaction between the substrate and ligand are based on our previous study on the enantioselective borylation reaction using a C_1 symmetric QuinoxP*-type bisphosphine ligand.[11] The trifluoromethyl group, in which one of the fluorine atoms acts as a leaving group, is situated at the sterically less hindered region (upper left) to avoid any steric repulsion (Figure 3a). This configuration leads to a favorable TS and gives the major enantiomer [(*S*)-**3a**]. However, there is steric repulsion between the trifluoromethyl group and adamantyl moiety around the upper left region in the unfavored TS (Figure 3b). Thus, this repulsion suppresses the formation of the disfavored configuration and (*R*)-**3a** was obtained as the minor enantiomer.

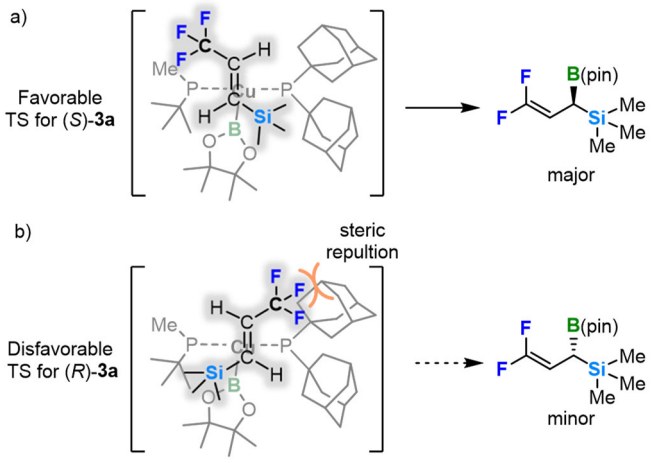


Figure 3. Proposed transition states determining the enantioselectivity of the reaction.

Conclusion

In summary, we have developed an enantioselective borylation of trifluoromethyl- and silyl-substituted alkenes using a QuinoxP*-type bisphosphine ligand in good yield with high enantioselectivity (up to 83% yield and 86% ee, respectively). This is the first synthesis of optically active *gem*-difluoro-1-silyl-allylboronates reported to date. The boron and silyl groups in the products were derivatized into a variety of functionalities, which exemplify their synthetic utility toward the preparation of structurally complex chiral fluorinated molecules that are difficult to obtain by other means.

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Keywords: borylation • copper • enantioselectivity • β-fluoroelimination • *gem*-difluoroalkenes

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[12] We observed that the reaction gave the product with between 76% ee and 86% ee. We suppose that this is caused by impurities in the substrate or the catalyst.

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[17] We used a different batch of the allylboronate (*S*)-**3a** with 76% ee for the Sonogashira coupling.

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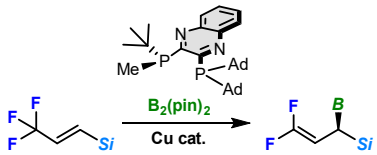

- ***Up to 83% yield, 86% ee***
- ***Novel organofluorine optically active building block***

Trifluoromethyl-substituted alkenyl silanes were converted into optically active *gem*-difluoro-1-silyl-allylboronates via a copper(I)-catalyzed borylation utilizing optically active, C_1 symmetric QuinoxP*-type bisphosphine ligands in good yield and enantioselectivity (up to 83% yield, 86% ee). The product of this reaction can be used as optically active organofluorine building blocks via further transformation.

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