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Transition-Metal-Free Defluorosilylation of Fluoroalkenes with Silylboronates

Pan Gao[a†], Guoqiang Wang[b†], Longlong Xi[a], Minyan Wang[a], Shuhua Li[b*], and Zhuangzhi Shi[a*]

ABSTRACT Silylated fluoroalkenes are important synthetic intermediates with complementary reactivity which play a key role in the construction of natural products, pharmaceuticals, and manmade materials. Converting the normally highly stable fluoroalkenes into silylated fluoroalkenes by selective defluorosilylation is a challenging task. Here, we report a simple, inexpensive and robust defluorosilylation of a variety of fluoroalkenes with silylboronates in the presence of alkoxy base to directly synthesize various silylated fluoroalkenes. The protocol features mild and safe reaction conditions that avoid a catalyst, a transition metal, a ligand, and high reaction temperature and tolerates a wide scope of fluoroalkene substrates without compromising the efficiency. Density functional theory calculations show that transient silyl anion complex undergoes a SN2′ or S_NV substitution which is responsible for this base-mediated defluorosilylation.

KEYWORDS metal-free , silane , fluorine, DFT, C-F activation

Introduction

Organic compounds containing a C–F bond play important roles in a variety of fields ranging from organic materials to drug discovery to agrochemical science.[1] These features have triggered the development of synthetic methods to complement existing strategies accessing these compounds. With the steady progress of methods for the preparation them, defluorinative functionalization of easily accessible fluorine-containing compounds[2] can provide facile access to complex fluorinated molecules, which have recently attracted increasing attention.[3]Among them, defluorosilylation has shown promises, because silyl groups can be readily converted into a wide variety of other functional groups.[4] In 2018, Shibata and coworkers reported the first Ni-catalyzed *ipso*-silylation of aryl fluorides via cleavage of unactivated C–F bonds, thereby streamlining access to aromatic silanes.[5]Interestingly, they found that alkyl fluorides could directly convert into the corresponding alkyl silanes mediated by an alkoxy base in the absence of the Ni catalyst. A catalyst-free strategy that does not require a transition metal to achieve the defluorosilylation is of great interest to chemists.[6]Shortly afterwards, Studer and Würthwein reported the development of readily generated silyl lithium reagents with aryl fluorides to provide the corresponding aryl silanes.[7] Meanwhile, Martin et al. developed a base-promoted defluorosilylation of unactivated fluoroarenes and fluoroalkanes by C-F bond cleavage.[8] Despite these advances, transition-metal-free defluorosilylation of fluoroalkenes to build silylated fluoroalkenes remains elusive.[9]

Fluoroalkenes are an important class of molecules, among which, *gem*-difluoroalkenes[10] and monofluoroalkenes are essential structural motifs in the design of medicinally active compounds, and these moieties have been used extensively as carbonyl and amide isosteres due to their similar steric and electronic profiles to these substituents.[11] As early in 1997, Tellier and coworkers reported a pioneering work on synthesis of *gem*-difluoroallylsilanes by copper-mediated allylic substitution of1-bromo-1,1-difluoro-2-alkenes with silyllithium reagents (Fig. 1a).[12] In 2018, copper-catalyzed defluorosilylative reaction of fluoroalkene feedstocks was developed,[13] in which the 1,2-addition of a silylcopper intermediate to the fluoroalkene and the subsequent selective β-F elimination is a key step for the success (Fig. 1b). Herein, we describe the development of a simple and universal method for the defluorosilylation of diverse

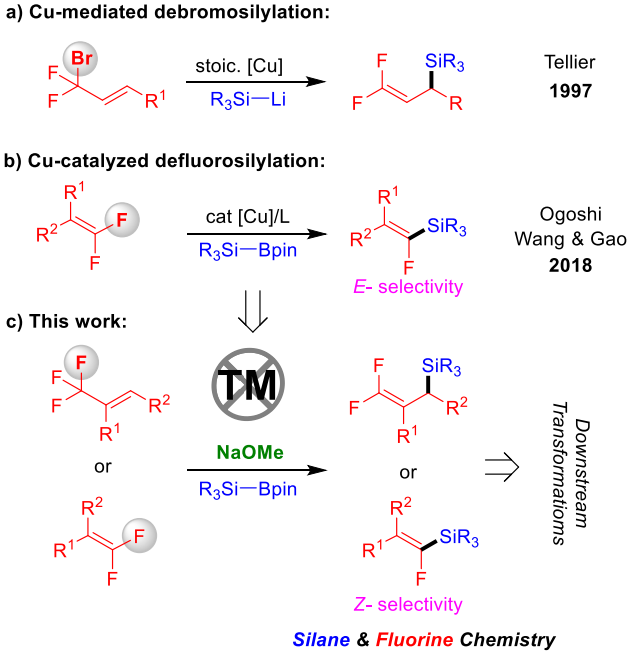

Figure 1 Development of a transition-metal-free system for defluorosilylation of fluoroalkenes.

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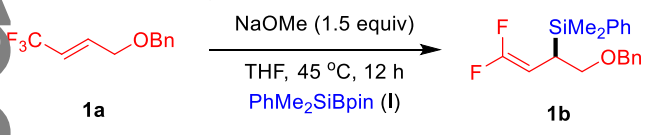
fluoroalkenes with silylboronates[14] to generate various silylated fluoroalkenes mediated by an only alkoxy base (Fig. 1c). Density functional theory calculations revealed that transient silyl anion complex undergoes SN2' or S_NV substitution was responsible for this base-mediated defluorosilylation reaction, thus obviating the need for copper salts.

Results

Reaction discovery. To begin our studies, we chose 1-(trifluoromethyl)alkene **1a** and commercially available Me_2PhSi-Bpin(**I**)as the model substrates (Table 1). After systematic optimization, using 1.5 equiv of NaOMe as a base, at 45 °C under an argon atmosphere in THF, defluorosilylation product **1b** was generated in 95% yield (entry 1). Other bases such as LiO^{t}Bu were also effective for this transformation (entry 2), but using NaOAc (entry 3) or Na_2CO_3 (entry 4) led to no conversion. A control experiment confirmed that the silylation process did not occur in the absence of the NaOMe (entry 5). These results indicated that the use of alkoxy bases were critical for success. The solvent effect was also pronounced. Other ether solvents like1,4-dioxane (entry 6) provided **1b** in excellent yield as well, but the reactions in DMF (entry 7) or toluene (entry 8) led to much lower conversions. Notably, lowering the reaction temperature to room temperature could also maintain a good reactivity (entry 9). Finally, the reaction could be conducted well in the dark, excluding a visible-light-driven process (entry 10).

Table 1. Reaction optimization.[a]



1a **1b**

Entry	Variation from the "standard conditions"	Yield of **1b** (%)[b]
1	none	95
2	Using LiOtBu instead of NaOMe	92
3	Using NaOAc instead of NaOMe	0
4	Using Na_2CO_3 instead of NaOMe	0
5	Without NaOMe	0
6	In 1,4-dioxane	93
7	In DMF	56
8	In toluene	35
9	At room temperature	86
10	In dark	94

[a]Reaction conditions: **1a** (0.20 mmol), **I** (0.30 mmol), and base (0.3 mmol) in solvent (1 mL) was stirred for 12 h at 45 °C under Ar. [b]Isolated yield after chromatography.

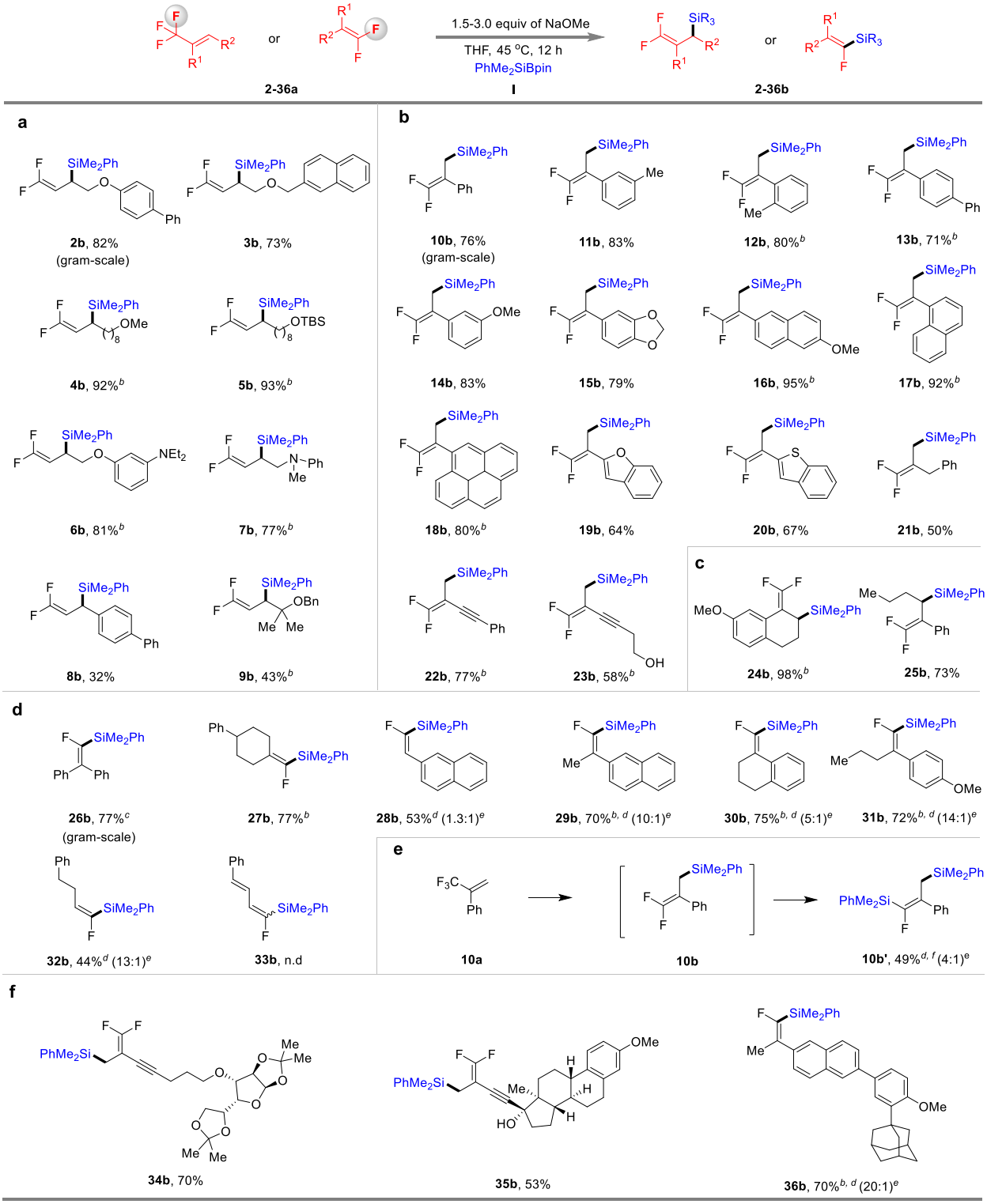
Scope of the methodology. With the optimized reaction conditions in hand, we first probed the reactivity of 1-(trifluoromethyl)alkenes with Me_2PhSi-Bpin(**I**) (Table 2a). Biphenyl (**2a**) and naphthyl (**3a**) groups on the substrates did not hinder the reactivity, and the reaction afforded corresponding products **2b**-**3b** in73-82% yields. Defluorosilylation of 1-(trifluoromethyl)alkenes with either OMe (**4b**) or OTBS (**5b**)moieties on a distal position proceeded smoothly. Notably, substrates with strongly coordinating groups, such as amine moieties, still underwent defluorosilylation to afford desired products **6**-**7b** in good yields. Whenβ-aryl-containing 1-(trifluoromethyl)alkenes such as **8a** were subjected to the optimized reaction conditions, we isolated defluorosilylative product **8b** in 32% yield. Interestingly, substrate **9a**, with an adjacent sterically bulky group, still afforded product **9b** in 43% yield.

Cu-catalyzed defluorosilylation of (3,3,3-trifluoroprop-1-en-2-yl)benzene (**10a**) with Me_2PhSi-Bpin (**I**) could produce product **10b** in excellent yield.[13a] Significantly, our catalyst-free system could perform the same transformation and provide 76% yield of **10b** in gram-scale (Table 2b). Other styryl substrates bearing *meta*- and *ortho*-methyl (**11**-**12b**), phenyl (**13b**), methoxy (**14b**), and 1,3-benzodioxole (**15b**) groups were all effectively transformed into their corresponding *gem*-difluoroalkenes. We also found that an array of π-extended systems participated in the reaction to afford defluorosilylative products **16**-**18b** in good yields. Moreover, the presence of heterocycles **19**-**20b** did not interfere with productive C–F bond cleavage. Besides that, benzyl substituted substrate **21a** was also tolerated. In addition, 2-trifluoromethyl-1,3-enynes underwent successful silylation to afford **22**-**23b** without concomitant addition to the alkynyl moiety. Notably, internal trifluoromethyl alkenes such as **24**-**25a** provided desired products **24**-**25b** in 73-98% yields (Table 2c).

This reaction system was not limited to trifluoromethylalkenes, *gem*-difluoroalkenes could also be compatible (Table 2d). Compared to the reported copper-catalyzed process,[13] our catalyst-free process exhibits some special reactivities and functional-group tolerances. This strategy is uniquely suited to sterically hindered tetrasubstituted *gem*-difluoroalkenes, such as **26**-**27a**, which are difficult substrates for transition-metal-catalyzed reactions. When *gem*-difluoroalkene **28a** was used, the reaction proceeded efficiently and generated the corresponding monodefluorosilylated product **28b** as a mixture of the *Z*/*E* regioisomers (1.3/1). Gratifyingly, with the additional alkyl-substituents (**29**-**31a**) installed, the ratio of *Z*selectivity was dramatically increased. Moreover, alkyl substituted *gem*-difluoroalkene such as **32a** also generated a *Z*-selective product **32b** in high stereoselectivity.[15] Unfortunately, the use of diene **33a** did not afford **33b** under our conditions. Apparently, *gem*-difluoroalkenes obtained from trifluoromethylalkenes can serve as substrates for further defluorosilylation to afford fluoro(silyl)alkenes when excess amounts of silylboronate are employed. For instance, dual silylation of 2-(trifluoromethyl)alkene **10a** could generate **10b'** as the major product via intermediate **10b** (Table 2e).

This strategy was also viable for the late-stage modification of complex molecules (Table 2f). For example, furanose derivative **34a** could undergo defluorosilylation with Me_2PhSi-Bpin (**I**) to produce product **34b** in 70% yield. Substrate **35a**, bearing a tertiary propargylic alcohol, was also readily transformed into 1,1-difluoro-1,3-enyne **35b** in 53% yield. *Gem*-difluoroalkene **36a** derived from Adapalene, a second-generation topical retinoid primarily used in the treatment of mild-moderate acne, can also be subjected to defluorosilylation to produce the fluoro(silyl)alkene **36b** in good yield.

Table 2. Substrate scope of fluoroalkenes.[a]



[a]Reaction conditions:A mixture of fluoroalkene **a** (0.20 mmol), silylboronate **I** (0.30 mmol), and NaOMe(0.30 mmol) in THF (1 mL) was stirred for 12 h at 45 °C under Ar, isolated yield after chromatography. [b]Fluoroalkene **a** (0.20 mmol), silylboronate **I** (0.60 mmol), and NaOMe(0.60 mmol). [c]At 60 °C. [d]Isolated yield of the major product. [e]Z/E ratio was deternined by ^{19}F NMR. [f]Fluoroalkene **a** (0.20 mmol), silylboronate **I** (1.2 mmol), and NaOMe(1.2 mmol) in THF (2 mL).

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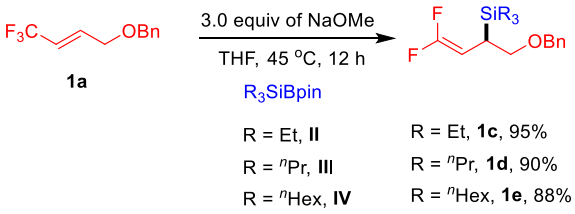
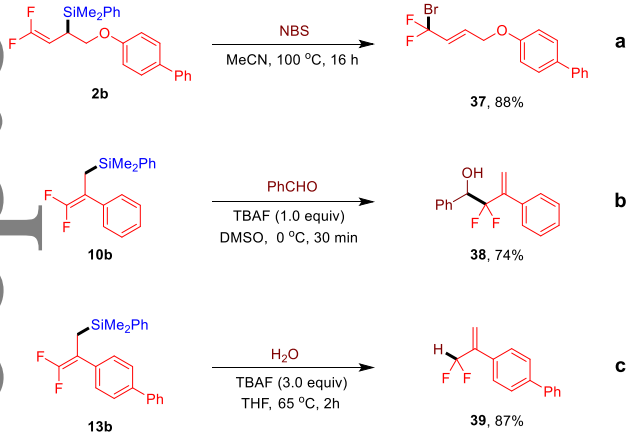
Several different silylboronates were also investigated as reaction partners under the optimized reaction conditions (Scheme 1). Alkyl-substituted silylboronates such as **II**-**IV** could react with 1-(trifluoromethyl)alkene **1a** to form a series of *gem*-difluoroallylsilanes **1c**-**1e** in good to excellent yields.



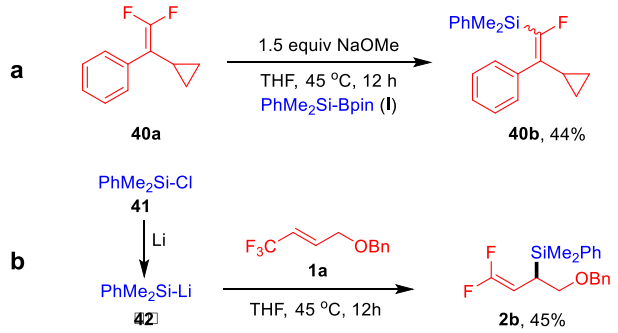
Scheme 1. Defluorosilylation of 1-(trifluoromethyl)alkene **1a** with different silylboronates **II**-**IV**.

Synthetic applications. The highly electron-rich allylic C-Si bond in the generated *gem*-difluoroallylsilanes can stabilize a positive charge at the β position through hyperconjugation. Electrophilic additions to these species can take advantage of this, and site selectivity generally reflects this property-electrophiles bind to the difluoromethylene γ to the silyl group. For instance, when generated product **2b** was treated with NBS, we isolated valuable 1-bromo-1,1-difluoro-2-alkene **37** in 88% yield (Scheme 2a).[16] Treatment of compound **10b** with benzaldehyde in the presence of TBAF could form a homoallylic alcohol **38** in 74% yield(Scheme2b). In addition, the reaction of silylated fluoroalkene **13b** with water and TBAF could affordCF_2H-substituted counterpart**39**in good yield (Scheme2c).[17]Therefore, this defluorosilylative process can act as a key step in the synthesis of various CF_2-substituted vinyl targets from easily accessible trifluoromethylalkenes.



Scheme 2. Synthetic applications.

To investigate the reaction mechanism, we first explored a radical clock experiment by performing the reaction on (1-cyclopropyl-2,2-difluorovinyl)benzene (**40a**). Under the standard conditions, we obtained normal silylated product **40b** in 44% yield, and no ring-opening product was detected (Scheme 3a). This result indicates that this silyl substitution reaction is not a radical-mediated pathway. Inspired by a recent work on defluorosilylation of fluoroarenes with silyl lithium, we utilized a pre-generated $Me_2PhSiLi$ reagent (**42**)[18] in this reaction affording the desired product **2b** in 45% yield (Scheme 3b). The result indicates that this free sily anion could be a possible intermediate in our system.[19]



Scheme 3. Mechanistic experiments.

Then, density-functional theory (DFT) with the M06-2X functional[20]was performed to probe the possible mechanism of this base-mediated defluorosilylation (see Supporting Information for details). As shown in Fig. 2, the heterolytic cleavage of B-Si bond in **IN1** generates silyl sodium with MeOBpin coordinated to the sodium cation **IN2**, which proceeds via $\mathbf{TSI_{N1/IN2}}$ with a barrier of 18.1 kcal mol^{-1}. The formation of **IN2** is endergonic by 16.7 kcal mol^{-1}, which is consistent with the experimental results that only a new signal corresponding to [($PhMe_2Si$)(MeO)Bpin]-(**IN1**) at 3.9 ppm could be detected by means of the ^{11}B NMR experiment and the 1:1 ratio of $PhMe_2SiBpin$ (δ = 33.1 ppm) and NaOMe in [D8]THF.[21] Next, the release of (MeO)Bpin accompany by the association of 1-(trifluoromethyl)alkene **1a** with $PhMe_2Si^-Na^+$ forms a loose complex **IN3**.[22] The subsequent nucleophilic attack of silyl anion on **1a** via $\mathbf{TS_{IN3/1b}}$ generates defluorosilylation product **1b** and NaF (pathway I). The $\mathbf{TS_{IN3/1b}}$, the nucleophilic addition of $PhMe_2Si^-$ to C=C bond and the elimination F anion occurs simultaneously, and therefore, could be characterized to a classical S_N2' transition state. The activation barrier this transition state is 27.4 kcal mol^{-1}, and the whole defluorosilylation reaction is exergonic by 26.6 kcal mol^{-1}. These results suggest that the studied reaction is thermodynamically and kinetically feasible under the experimental conditions. However, the alternative pathway involves the direct nucleophilic attack of the silyl atom of **IN1** on the double bond of **1a** can be excluded by its high activation barrier (pathway II, ΔG ≠ for $\mathbf{TS_{IN1}/1b}$>43.7 kcal mol^{-1}). On the basis of these results, the pathway involving the transient silyl anion complex through a S_N2' substitution is responsible for this base-mediated defluorosilylation reaction of trifluoromethylalkenes.

Notably, defluorosilylation of *gem*-difluoroalkenes is calculated to proceed *via* a S_NV pathway,[23] which is mechanistically different from trifluoromethylalkenes. As shown in Fig. 3a, two four-membered transition states, ***Z*-$\mathbf{TS_{IN4}}$/29b** and ***E*-$\mathbf{TS_{IN4}}$/29b**, are responsible for the formation of ***Z*-29b** and ***E*-29b**, respectively. With the *gem*-difluoroalkene **29a** as the model substrate, the *Z*-defluorosilylation pathway (***Z*-$\mathbf{TS_{IN4}}$/29b**) is kinetically more favorable than the *E*-defluorosilylation pathway (***E*-$\mathbf{TS_{IN4}}$/29b**) by 1.1 kcal mol^{-1}. The stabilization of ***Z*-$\mathbf{TS_{IN4}}$/29b** benefits from delocalization of the negative charge in the transition state, indicated by small dihedral angle (-0.3° in ***Z*-$\mathbf{TS_{IN4}}$/29b** versus -29.8° in ***E*-$\mathbf{TS_{IN4}}$/29b,** see Fig. 3b). Therefore, the more stabilized *Z*-S_NV transition state leads to a preference for the occurrence of defluorosilylation reaction at the steric congested side of *gem*-difluoroalkenes.

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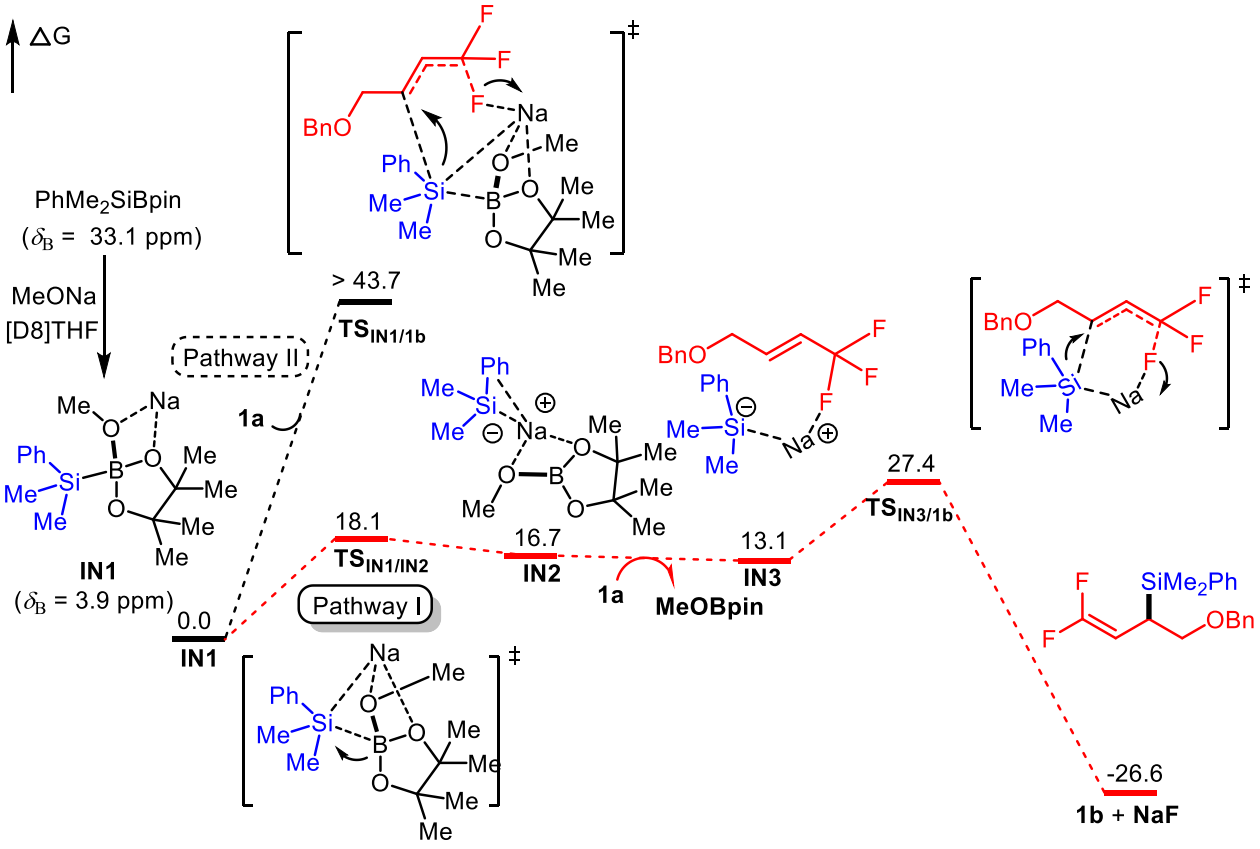

Figure 2. Computed free-energy surfaces for the model reaction between 1-(trifluoromethyl)alkene **1a** and silyborane/alkoxy base complex **IN1** (in kcal mol^{-1}).

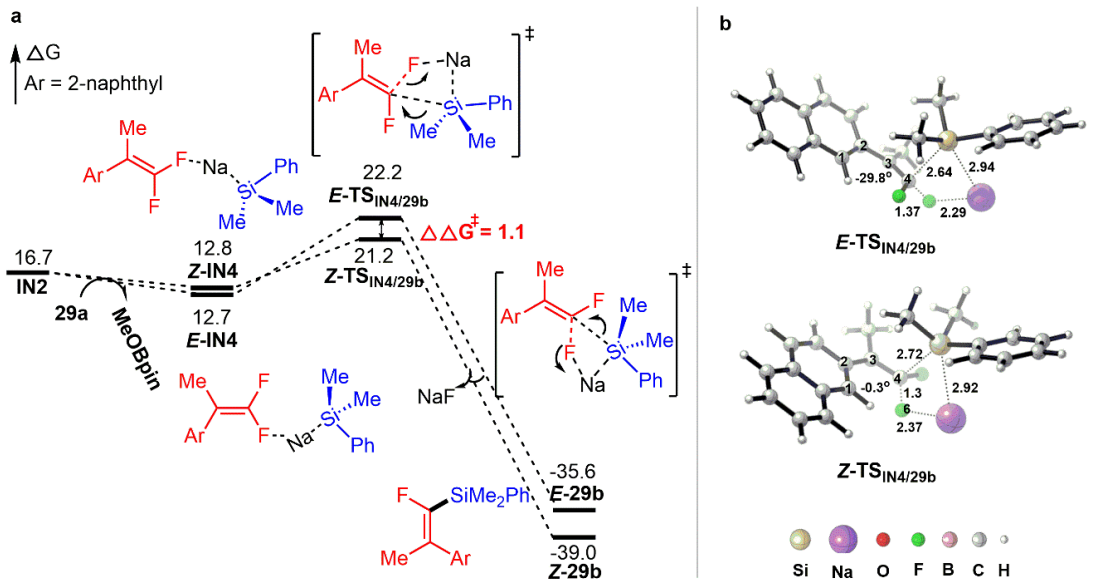

Figure 3.a Computed free-energy profiles of the reaction between *gem*-difluoroalkene **29a** and silylboronate/alkoxy base complex **IN2** (in kcal mol^{-1}). b 3D-structures of *Z*- and *E*- SN^V transition states.

Conclusions

In summary, we have developed an efficient catalyst-free system that can activate the C–F bonds of diverse fluoroalkenes via a defluorosilylation process to produce a series of silylated fluoroalkenes. The distinct mechanistic platform and the resulting mild and environmentally friendly reaction conditions allow the incorporation of a variety of synthetically useful functional groups into the coupling partners. We anticipate that this transition-metal-free strategy based on well-developed silane chemistry will simplify the synthesis and structural elaboration of

gem-difluoroalkene and monofluoroalkene targets for research in chemistry, biology and medicine.

Experimental

To a 25 mL Schlenk tube was purged with argon for three times, and then added fluoroalkenes **1a** (43.2 mg, 0.2 mmol), $PhMe_2SiBpin$ (**I**, 78.6 mg, 1.5 equiv), NaOMe (16.2 mg, 1.5 equiv) and THF (1 mL). The formed mixture was stirred at 45 ^{o}C under argon for 12 h monitored by TLC. The solution was then cooled to room temperature and the solvent was removed under vaccum directly. The crude products were purified by column chromatography on silica gel to afford product **1b** (61.8 mg, 93%) as a colorless liquid.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2018xxxxx.

Acknowledgement

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[22] The pathway involving the association of MeOBpin in the defluorosilylation transition state is predicted to be 30.9 kcal mol-1 which is higher than TSIN3/1b (see SI in Figures S6-7 for details).

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Entry for the Table of Contents

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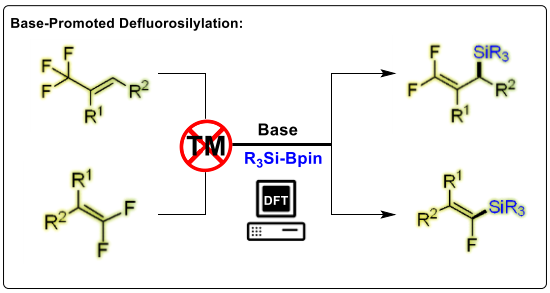
Transition-Metal-Free Defluorosilylation of Fluoroalkenes with Silylboronates



Pan Gao[a†], Guoqiang Wang[b†], Longlong Xi[a], Minyan Wang[a], Shuhua Li[b*], and Zhuangzhi Shi[a*]

A mild, catalyst-free system has been established for the defluorosilylation of various fluoroalkenes with silylboronates via C-F activation. This route employs an inexpensive alkoxy base and can be used to generate silylated fluoroalkenes with a variety of synthetically useful functional groups.

