Organic LETTERS

Radical Silyldifluoromethylation of Electron-Deficient Alkenes

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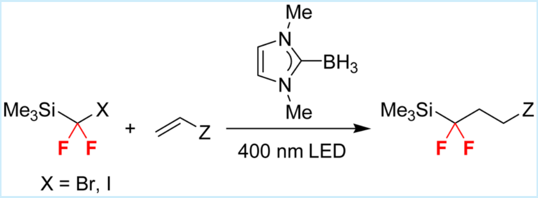
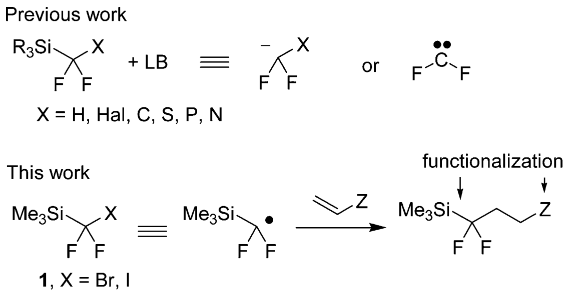
S *Supporting Information*

ABSTRACT: A reaction of bromo- and iododifluoromethyl-substituted silanes with electron-deficient alkenes in the presence of an N-heterocyclic carbene borane complex is described. The reaction is performed under irradiation with light-emitting diodes and proceeds via a radical chain mechanism. The resulting products, the functionalized silicon reagents, can undergo chemoselective transformations involving either the silyldifluoromethyl fragment or the functional group.



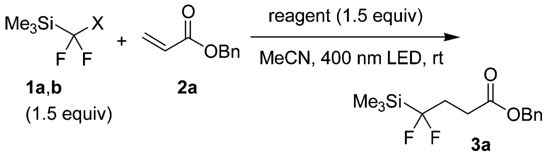
Widespread applications of organofluorine compounds in drug development[1] have spurred the elaboration of methods for their synthesis.[2] Fluorinated silicon reagents have become valuable tools for the direct introduction of a perfluorinated[3] or a partially fluorinated[4] fragment into organic molecules. The reactions with these silanes are, typically, performed under Lewis basic conditions, which are required to effect cleavage of the Si−C bond. In these processes, the silanes serve as sources of either the corresponding carbanionic species[3] or difluorocarbene[5] (Scheme 1). Herein, we report the use of bromo- and iodo-substituted difluorinated silanes **1** in free-radical coupling with electron-deficient alkenes, affording products of hydrofluoroalkylation.[6,7] We also demonstrate that products of the silyldifluoromethylation reaction can be further functionalized selectively at the Si−C bond or at the terminal group.

Scheme 1. Application of Fluorinated Silanes



Homolytic cleavage of the carbon−halogen bond is usually effected using toxic tin hydride or expensive tris(trimethylsilyl)silane.[8] In 2008, it was reported that alkyl iodides react with electron-deficient alkenes in the presence of sodium cyanoborohydride under irradiation with a powerful xenon arc lamp.[9] In our work, as a starting point, we evaluated a reaction of commercially available (bromodifluoromethyl)trimethylsilane[10,11] (Me_3SiCF_2Br, **1a**) with benzyl acrylate, applying various boron hydrides.[12] The reactions were irradiated using 400 nm light-emitting diodes with the temperature maintained around 25 °C by external cooling (Table 1). With a cyanoborohydride anion, product **3a** was formed in moderate yields (entries 1 and 2). Variation of hydride source allowed us to identify N-heterocyclic carbene borane complex (*N*,*N*′-dimethylimidazolydene borane, $NHC{\cdot}BH_3$)[12b,13] as a suitable reagent, providing product **3a** in 57% yield. Further increase in yield was achieved by switching to more reactive iodo-substituted silane **1b**.

Table 1. Reaction of Silanes with Benzyl Acrylate



no.	X	reagent	time, h	yield of **3a** (%)[a]
1	Br	$NaBH_3CN$	3	42
2	Br	$Bu_4N{\cdot}BH_3CN$	3	27
3	Br	$py{\cdot}BH_3$	3	
4	Br	$Me_3N{\cdot}BH_3$	3	
5	Br	$NHC{\cdot}BH_3$	3	57 (57)[b]
6	I	$NHC{\cdot}BH_3$	2	89 (85)[b]

[a]Determined by NMR or GC analysis of reaction mixtures. [b]Isolated yield.

Under the optimized conditions, a series of electron-deficient alkenes were silyldifluoromethylated using NHC-borane complex. As iodo-substituted silane **1b** is obtained from **1a** by a tedious protocol,[14] reactions were, typically, first evaluated with silane **1a** (Table 2). As a rule, products **3** were formed in reasonable yields with esters and *N*,*N*-disubstituted amides. For

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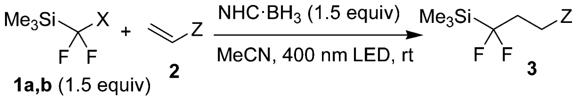
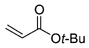
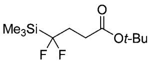
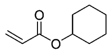
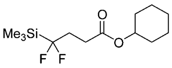
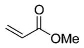
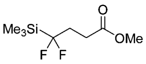
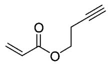
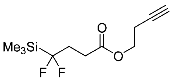
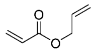
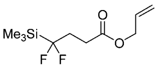
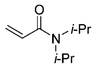
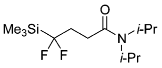
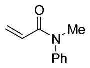
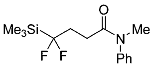
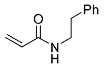
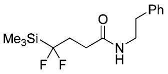
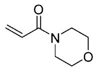
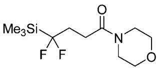
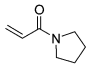
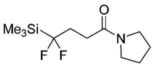
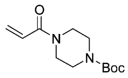
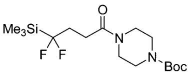
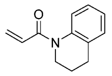
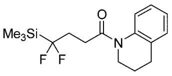
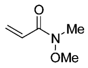
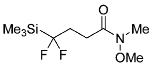
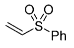
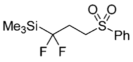
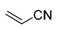
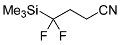
Table 2. Silyldifluoromethylation of alkenes 2[a]



no.	alkene	product	3	X	yield (%)[b]
1			**3b**	Br	73
2			**3b**	I	77
3			**3c**	Br	71
4			**3d**	Br	46[c] (72)[d]
5			**3e**	Br	50
			3e	I	59
6			**3f**	Br	45[c] (57)[d]
7			**3g**	Br	75
8			**3h**	Br	75
9[e]			**3i**	Br	31
10			**3i**	I	54
11			**3j**	Br	72
12			**3k**	Br	51
13			**3k**	I	49
14			**3l**	Br	64
15			**3m**	Br	62
16			**3n**	Br	59
17			**3n**	I	43[d]
18			**3o**	Br	77
19			**3p**	Br	41
20			**3p**	I	60[c] (66)[d]

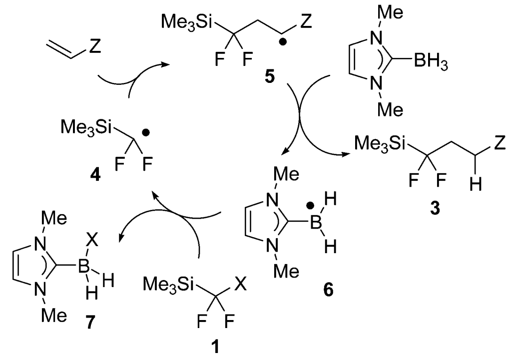
[a]Reaction time: for **1a**, X = Br, 3 h; for **1b**, X = I, 2 h. [b]Isolated yield. [c]Isolated yield is decreased due to product volatility. [d]Determined by NMR analysis of reaction mixture. [e]2 equiv of **1a** was used.

amide bearing an N—H bond, silane **1b** must be used to achieve efficient reaction (entries 9 and 10). At the same time, for Weinreb amide, bromo-substituted silane **1a** gave higher yield of the product compared to that of the iodinated counterpart (entries 16 and 17). Interestingly, in reactions of allyl and homopropargyl acrylates, only expected products **3e**,**f** were formed (entries 5 and 6), and no cyclization products were observed. Phenyl vinyl sulfone and acrylonitrile reacted successfully, furnishing corresponding products (entries 18—20). Di- and trisubstituted acrylates were markedly less reactive. Thus, in reactions of methyl crotonate and methyl (*E*)-2-methylbut-2-enoate with silane **1a**, less than 20% of expected products were formed. For methyl vinyl ketone, no addition product was observed, presumably due to the reduction of the enone system with NHC-borane.[15]

Silanes **3** are air-stable liquid or solid compounds, which can be purified by conventional column chromatography on silica gel. The structure of silane **3g** was verified by X-ray diffraction analysis.

Concerning the mechanism, we believe that the reaction proceeds via a radical chain process (Scheme 2). Silyldifluoromethyl radical **4** attacks the double bond, generating radical **5**, which abstracts hydrogen from NHC-borane, leading to boryl-centered radical **6**.[16] The latter species abstracts the halogen atom from silanes **1**, regenerating radical **4** along with formation of haloborane byproduct **7**. The scheme would be successful if NHC-borane reacts faster with radical **5** than with radical **4**. This assumption is supported by earlier calculations of B—H bond cleavage by a radical, suggesting much greater reactivity of an ester-substituted radical compared to that of an alkyl radical.[9b] Nevertheless, in our case, the reduced silane Me$_3$SiCHF$_2$ is observed in reaction mixtures in small amounts (less than 10%). An alternative mechanism for the formation of product **3** would be a SET reduction of radical **5** followed by abstraction of a proton from the solvent. However, when the reaction of **1a** with *tert*-butyl acrylate (**2b**) and NHC-borane was performed in CD$_3$CN, no incorporation of the deuterium in the product was observed (NMR and GC-MS control).

Scheme 2. Proposed Mechanism



The reaction is completely blocked if TEMPO (1.5 equiv) is added, thereby corroborating the involvement of radical intermediates. The progress of the NHC-borane-mediated reaction of bromo-substituted silane **1a** with *tert*-butyl acrylate (**2b**) was monitored in a light/dark sequence (Figure 1). The reaction proceeds during periods when the light is turned off, which supports the chain mechanism.

A challenging question for this reaction is how it is initiated. In a report on a cyanoborohydride-mediated process, it was proposed that the carbon—iodine bond of alkyl iodides is homolytically cleaved with UV light.[9a] However, homolysis of the carbon—bromine bond of **1a** with 400 nm light seems less likely.[17] At the same time, light is important for reaction efficiency. Thus, in the absence of light, the reaction of silane **1a** with *tert*-butyl acrylate **2b** performed under typical conditions (argon atmosphere) gave product in 36% yield (Scheme 3). The same dark reaction but under air atmosphere proceeded similarly. In an attempt to exclude oxygen, the starting mixture was degassed by triple freeze—thaw cycles followed by filling the vessel with argon, and the product was formed in 14% yield.

To evaluate the effect of fluorine, silane **1a** was compared with nonfluorinated analogue **8** under the same conditions (Scheme

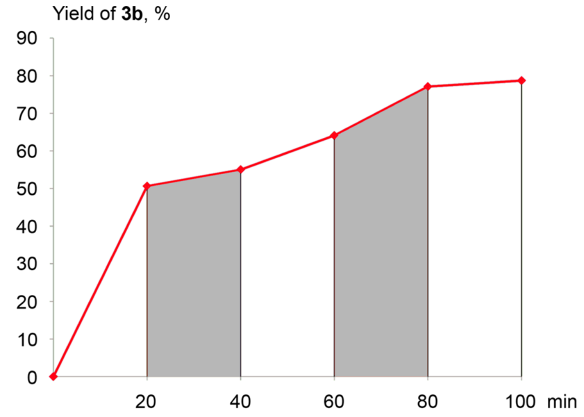
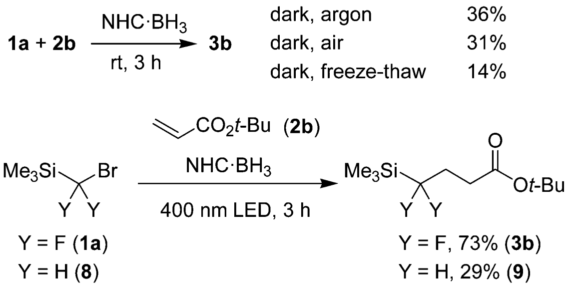


Figure 1. Light/dark sequence for the reaction of **1a**, **2b**, and NHC-borane. Dark periods are shown in gray.

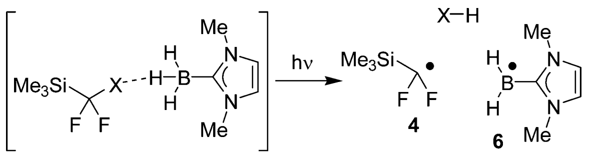
Scheme 3. Mechanistic Experiments



3, bottom equation). In reaction with *tert*-butyl acrylate **2b**, difluorinated silane **1a** was notably more reactive. Given that C—Br bond dissociation energies are similar for fluorinated and nonfluorinated bromides,[18] the observed accelerating effect of fluorine is remarkable.

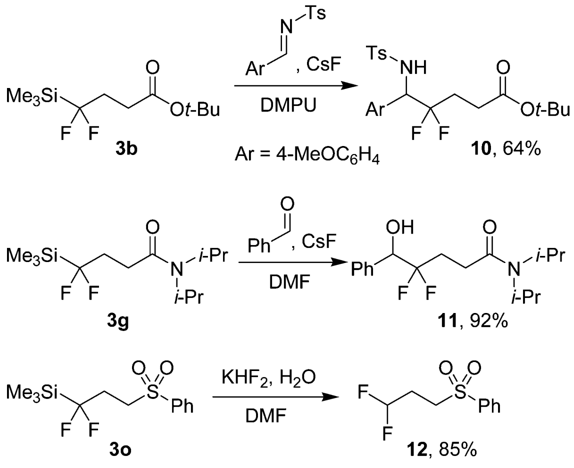
On the basis of available observations, we may propose the formation of a complex between the silane and the borane (Scheme 4). Two fluorine atoms provide greater stability to this species featuring attractive halogen—hydride interaction.[19] Under the action of light, the complex can undergo homolytic fragmentation, generating radicals **4** and **6**, which can lead a chain reaction.[20,21]

Scheme 4. Proposed Initiation Step

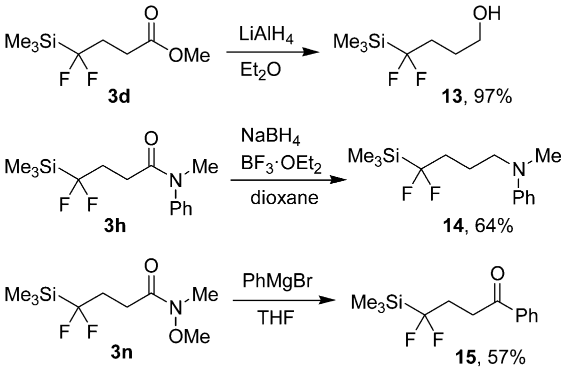


Compounds **3** contain two reactive sites—the carbon—silicon bond and a functional group, and it would be interesting to develop conditions for chemoselective transformations. The fragment of *gem*-difluorinated silane can be reacted with *N*-tosyl imine or aldehyde in the presence of fluoride anion (Scheme 5). Protodesilylation of silane proceeded cleanly when water was added in the reaction mixture, furnishing product **12** bearing the difluoromethyl group.

Scheme 5. Reactions at the C—Si Bond



Scheme 6. Reactions at the Functional Group



Reactions at the functional group without affecting the Me_3SiCF_2 fragment are shown in Scheme 6. Reduction of the ester group was cleanly performed using lithium aluminum hydride. For deoxygenation of amide **3h**, a procedure involving in situ generation of borane was employed.[22] Finally, compound **3n** bearing a Weinreb amide fragment was converted to the corresponding ketone upon reaction with phenyl magnesium bromide. These transformations provide access to new functionalized fluorinated silicon reagents **13—15**.

In summary, a convenient method for the silyldifluoromethylation of electron-deficient alkenes is described. The use of NHC-borane in combination with irradiation is important for the reaction efficiency. The method provides straightforward access to a family of functionalized *gem*-difluorinated silanes, which can further undergo chemoselective transformations.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01334.

Experimental procedures, compound characterization data, copies of NMR spectra for all compounds (PDF)
X-ray data for **3g** (CIF)

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Notes

The authors declare no competing financial interest.

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