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Siladifluoromethylation and Difluoromethylation onto C(sp^3), C(sp^2), and C(sp) Centers Using Ruppert–Prakash Reagent and Fluoroform

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Supporting Information

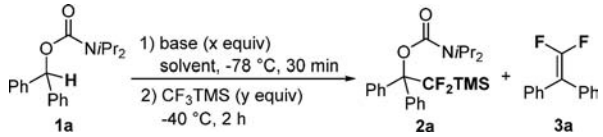
ABSTRACT: Siladifluoromethylations and difluoromethylations on sp^3, sp^2, and sp carbons of lithiated carbamates, arenes, and terminal alkynes, respectively, have been attained by employing the Ruppert–Prakash reagent (CF_3TMS) and fluoroform (CF_3H) as the CF_2 sources. The advantage of this reaction is that the (sila)difluoromethylated compounds can be obtained by simple treatment of easily accessible substrates, lithium bases, and CF_3TMS or CF_3H. Furthermore, the products bearing the TMS group can be transformed into the valuable compounds with the CF_2 fragment via the carbon–carbon bond forming reactions.

Organofluorine chemistry has become a major research field in the discovery of new bioactive molecules and materials,[1] and major efforts have focused on the introduction of a fluorine atom[2] and various perfluoroalkyl groups containing the CF_3 group.[3] Furthermore, attraction for organofluorine compounds possessing difluoromethylene ($-CF_2-$) and difluoromethyl ($-CF_2H$) groups is growing in pharmaceutical and agrochemical industries.[4] Actually, it has been proposed that the CF_2 fragment can be employed as an oxygen surrogate.[4]

The synthesis of compounds containing the CF_2 fragment can be conventionally performed via the deoxofluorination reaction[5] with harsh reagents such as *N*,*N*-diethylaminosulfur trifluoride (DAST) and derivatives of DAST or the building block method[6] using fluorinated starting materials. However, introduction of the CF_2 fragment based on the carbon–carbon bond formation has been less explored, in sharp contrast to the development of various methods to fluorofunctionalize. Recently, we succeeded in the α-difluoromethylations and α-siladifluoromethylations of carbonyl and nitrile compounds in the presence of a lithium base by using fluoroform (CF_3H)[3a,7,8] and the Ruppert–Prakash reagent (CF_3TMS)[9] as CF_2 sources.[10−12] We herein report the siladifluoromethylations and difluoromethylations on C(sp^3), C(sp^2), and C(sp) centers with lithiated carbamates, arenes, and terminal alkynes. The advantage of the reaction is that the simple combination of substrate, lithium base, and CF_3TMS or fluoroform can be converted to valuable compounds with the CF_2 fragment.

Siladifluoromethylation on a C(sp^3)[13] center was initiated by employing carbamate **1a**,[14] which was subjected to reaction conditions similar to those attained by our previous works[10b,c] (Table 1). Upon treatment with *n*-BuLi (1.0 equiv) in THF, the reaction of lithiated **1a** and CF_3TMS (5 equiv) provided the expected product **2a** in 21% yield,[15] along with *gem*-difluoroolefinated byproduct **3a** in 5% yield (Table, entry 1). Additionally, employment of 2 equiv of *n*-BuLi was found to enhance the yield of **2a**, although **3a** was also increased (Table 1, entries 2 and 3). An excess amount of CF_3TMS (10 equiv) could not improve the yield (Table 1, entry 4). While the selection of Et_2O instead of THF as a solvent led to no product (Table 1, entry 5), the mixed solvent of THF and Et_2O in a 1:1 ratio improved slightly the yield (50%) (Table 1, entry 6). The reaction was sensitive to lithium bases, and *n*-BuLi gave the best results (Table 1, entry 6 vs 8–11). The reaction of isolated **2a** and *n*-BuLi in THF at −40 °C did not afford **3a**, but **2a** in the presence of KF smoothly underwent the transformation into **3a**. The results strongly indicate that difluoromethyl lithium species (RCF_2Li) as the intermediate, which can lead to **2a** and **3a** via the trimethylsilylation by CF_3TMS and the β-elimination

Table 1. Siladifluoromethylation Using CF_3TMS



entry	base	*x*	*y*	solvent	yields of **2a**/**3a** (%)[b]
1	*n*-BuLi	1	5	THF	21/5
2	*n*-BuLi	2	5	THF	42/22
3	*n*-BuLi	2	2	THF	31/32
4	*n*-BuLi	2	10	THF	43/21
5	*n*-BuLi	2	5	Et_2O	0/18
6	*n*-BuLi	2	5	THF/Et_2O	50/26
7[a]	*n*-BuLi	2	5	THF/Et_2O	44/49
8	*s*-BuLi	2	5	THF	23/1
9	MeLi	2	5	THF	20/9
10	LDA	2	5	THF	0/0
11	LHMDS	2	5	THF	0/0

[a]Reaction temperature was −20 °C. [b]Yields were determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard.

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of carbamate group, respectively, is involved in the reaction mechanism.[10c]

With the optimized reaction conditions in hand, we explored the scope of substrates (Figure 1). The yields in the range of

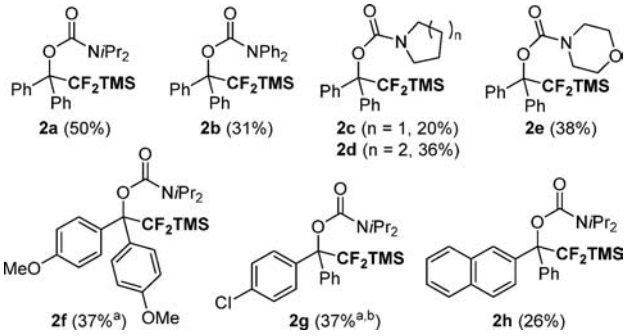
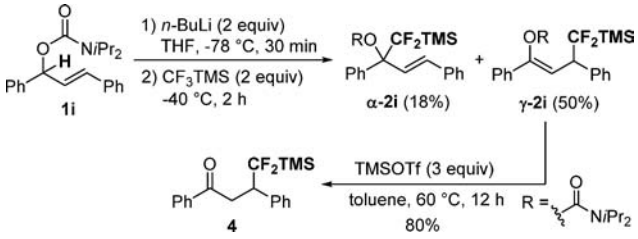


Figure 1. Siladifluoromethylation on sp^3 carbon. Reaction conditions: After reaction of *n*-BuLi (0.2 mmol) and **1** (0.1 mmol) in THF/Et_2O (0.5/0.5 mL) for 30 min at −78 °C, CF_3TMS (0.5 mmol) was added at −78 °C, and then the reaction mixture was stirred for 2 h at −40 °C. Isolated yields. [a] THF as a solvent was used. [b] Reaction temperature was −78 °C after addition of CF_3TMS.

20−50% (**2a**−**e**) were obtained for substrates bearing different carbamate moieties. Additionally, the reaction of carbamates with not only electron-donating but also electron-withdrawing substituents on the aryl rings was allowed to furnish the products **2f**−**h**, while the yields were not good.

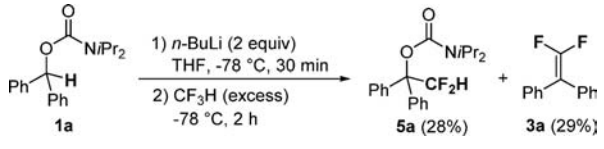
β,*γ*-Unsaturated carbamate **1i** readily derived from the corresponding allyl alcohol was also suitable in the present reaction. The reaction led to *γ*-siladifluoromethylated product ***γ*-2i** in 50% yield, along with *α*-siladifluoromethylated product ***α*-2i** in 18% yield (Scheme 1). The deprotection with TMSOTf of ***γ*-2i**, which was separated by silica-gel column chromatography, afforded the corresponding ketone **4** in 80% yield.

Scheme 1. Siladifluoromethylation on the *γ*-Position



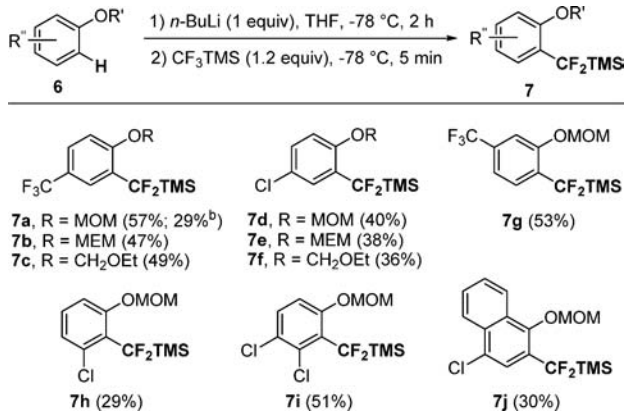
Furthermore, the difluoromethylation using fluoroform (CF_3H) instead of CF_3TMS as the CF_2 sources was conducted (Scheme 2). As expected, the bubbling operation of fluoroform to a THF solution of **1a** and *n*-BuLi (2 equiv) provided the desired *α*-difluoromethylated product **5a** in 28% yield, in spite of production of **3a** in 29% yield.

Scheme 2. Difluoromethylation on sp^3 Carbon Using CF_3H



We next envisioned that this method would be adaptable to siladifluoromethylation on the $C(sp^2)$[16] center using the Ruppert−Prakash reagent (Scheme 3). The reaction by

Scheme 3. Siladifluoromethylation on sp^2 Carbon



[a]Reaction conditions: After reaction of *n*-BuLi (0.2 mmol) and **6** (0.2 mmol) in THF (1.0 mL) for 2 h at −78 °C, CF_3TMS (2.2 mmol) was added at −78 °C, and then the reaction mixture was stirred for 5 min at −78 °C. Yields were determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard. [b]*n*-BuLi (2 equiv) was used.

treatment of aromatic substrates **6** bearing an alkoxyl directing-group proceeded to provide the corresponding arenes **7**, although the yields were not sufficiently high.[17] In contrast to the reaction with carbamate **1**, it was demonstrated that employment of 1 equiv of *n*-BuLi was optimal.[15] Under the reaction conditions, phenols **6a**−**f** protected by MOM, MEM, and CH_2OEt led to moderate yields (36−57%). The reaction of 4-(trifluoromethyl)phenol without MOM under the same reaction conditions resulted in recovery of the substrate. Phenol and naphthol derivatives **6g**−**j** bearing the electron-withdrawing substituents in the *m*- and/or *p*-positions was examined to afford the siladifluoromethylated arenes. Unfortunately, phenols protected by MOM bearing the electron-donating substituents, such as *tert*-butyl and methoxy groups, in the *p*-positions were transformed not to the desired products but to the trimethylsilylated arenes as sole products under the same reaction conditions. In addition, the reaction of **6a** with CF_3H in lieu of CF_3TMS in the presence of *n*-BuLi (1.0−2.0 equiv) resulted in the complete recovery of **6a**, because the protonation of aryl lithium species by CF_3H is preferred rather than the desirable C−C bond formation.

The success of aromatic siladifluoromethyaltion prompted us to investigate the transformation of the product into the difluoromethylated compounds with a variety of functional groups (Scheme 4). The methylation and esterification of **7a** employing MeI and ethyl chloroformate as electrophiles proceeded through the activation of silyl functionality in the presence of KF, providing the corresponding products **8** and **9**, respectively. Compound **7a** was also converted to the corresponding alcohol **10** and thioether **11**, by treatment of benzaldehyde and disulfide, respectively. Moreover, it was found that hexafluorobenzene underwent the pentafluoroarylation to give the unique polyfluoroarylated product **12** in 69% yield.

Finally, our method was also successfully applied to siladifluoromethylation on the C(sp)[18,19] center with terminal alkynes **13** (Scheme 5). After the best reaction conditions were

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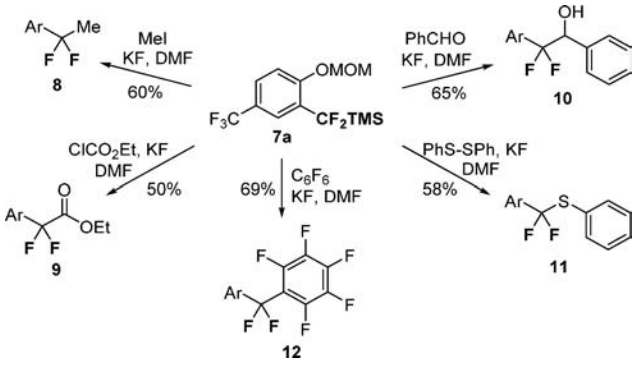
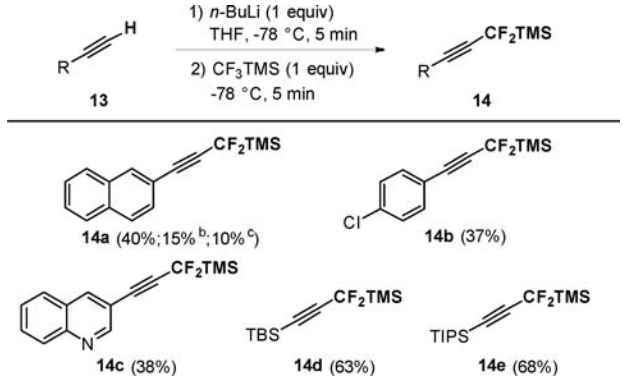
Scheme 4. Applications to Transforming Reactions



Scheme 5. Siladifluoromethylation on sp Carbon

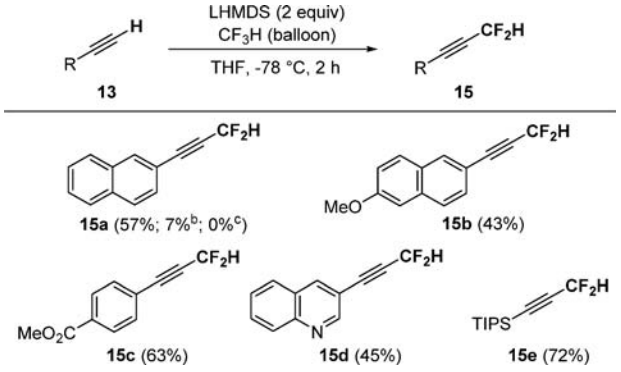


[a]Reaction conditions: After reaction of *n*-BuLi (0.2 mmol) and **13** (0.2 mmol) in THF (1.0 mL) for 5 min at −78 °C, CF_3TMS (0.2 mmol) was added at −78 °C, and then the reaction mixture was stirred for 5 min at −78 °C. Yields were determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard. [b]*n*-BuLi (2 equiv) was used. [c]LHMDS (1 equiv) instead of *n*-BuLi was used at rt for 1 h.

surveyed, the siladifluoromethylation using 1 equiv of *n*-BuLi and the Ruppert−Prakash reagent was found to give the highest yield of products.[15] Aromatic alkynes **13a−c** led to the corresponding products **14a−c** in less than 5 min. Additionally, the yields of **14d−e** endowed with sterically more demanding silyl-substituents increased to more than 60%. We were delighted to find that the difluoromethylation of **13** under a fluoroform atmosphere worked well with LHMDS (2 equiv) instead of *n*-BuLi as a lithium base (Scheme 6).[12] A variety of lithium bases such as LDA, LTMP, NHMDS, and KHMDS were also investigated, but no reaction proceeded. Moreover, the reaction method by bubbling of fluoroform to a THF solution of lithium acetylide, as shown in Scheme 2, led to a decrease in the yield. Under the reaction conditions at −78 °C, terminal alkynes **13** possessing not only (hetero)aryl groups but also a silyl one underwent the difluoromethylation to provide the corresponding products **15** in 43−72% yields. It is widely accepted that the alkynes **14** and **15** can be readily converted to various difluoromethylated building blocks.[19,20]

In summary, we have disclosed that the direct siladifluoromethylations onto $C(sp^3)$, $C(sp^2)$, and C(sp) centers by combination of carbanions with lithium as a countercation and the Ruppert−Prakash reagent can proceed through simple operations, providing the siladifluoromethylated carbamates, arenes, and alkynes, respectively. Especially, siladifluoromethylated arenes were exchanged to valuable difluoromethyl

Scheme 6. Difluoromethylation on sp Carbon of Alkyne



[a]Reaction conditions: After reaction of LHMDS (0.2 mmol) and **13** (0.1 mmol) in THF (1.0 mL) at −78 °C under excess amounts of CF_3H (1 atm: balloon), the reaction mixture was stirred for 2 h at −78 °C. Yields were determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard. [b]LHMDS (1 equiv) was used. [c]*n*-BuLi (2 equiv) instead of LHMDS was used.

building blocks. At the same time, we have also demonstrated that the difluoromethylations onto $C(sp^3)$ and C(sp) took place by employing the same lithium species and fluoroform. Development of novel catalytic (sila)difluoromethylations using the transition metal is ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01476.

Experimental procedures and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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(15) Recently, we have reported the α-difluoromethylation in the α-position of nitriles (for example, 2,2-diphenylacetonitrile) with Ruppert–Prakash reagent (CF_3TMS) under the similar reaction conditions (see ref 10c). In this case, addition of 1 equiv of *n*-BuLi to nitrile substrates did not undergo the reaction, because lithiated substrates (lithium ketene imine) cannot activate CF_3TMS. In sharp contrast, lithiated carbamates, arenes, and terminal alkynes, which possess higher nucleophilicity, can activate CF_3TMS to generate lithium carbenoid (CF_3Li) as active species in the present reactions.

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(17) The products **7b**, **7e**, and **7j** could not be isolated from impurities by silica-gel column chromatography. Therefore, the difluoromethyl compounds obtained by the following desilylation (treatment with 10% K_2CO_3 in MeOH) of the products were identified after the isolation by silica-gel column chromatography, respectively (**7b**, 35%; **7e**, 14%; **7j**, 26%); see Supporting Information.

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