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α-Difluoromethylation on sp^3 Carbon of Nitriles Using Fluoroform and Ruppert−Prakash Reagent

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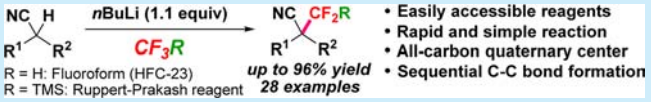
Supporting Information

ABSTRACT: Difluoromethylation on sp^3 carbon of various nitrile compounds with lithium base and fluoroform (CF_3H), which is an ideal difluoromethylating reagent, is shown to provide the α-difluoromethylated nitrile products with an all-carbon quaternary center in moderate to high yields. The Ruppert−Prakash reagent (CF_3TMS) is also applicable to the reaction, affording the α-siladifluoromethylated nitrile products, which can be utilized for sequential carbon−carbon bond-forming reactions. These reactions using 1.1 equiv of lithium base, 1.5−2.0 equiv of CF_3H or CF_3TMS, and easily accessible nitrile derivatives are completed in only a few minutes, resulting in the formation of valuable difluoromethylated compounds.



Fluoroform (also called trifluoromethane, CF_3H, and HFC-23) is mainly produced as a byproduct during chlorodifluoromethane manufacturing utilized in the production of Teflon (DuPont) but also readily manufactured via fluorine/chlorine exchange of chloroform.[1] While a nontoxic and nonozone-depleting gas (boiling point: −83 °C), it must be destroyed or transformed to environmentally benign compounds because it possesses a global warming potential 11700 times higher than that of CO_2.[1] Therefore, the development of a transformation of fluoroform to valuable and/or novel fluoromethylated building blocks has attracted much attention in view of not only pharmaceutical and agrochemical industries but also synthetic challenges to its low reactivity. However, in the past few years, the exploration of precise organic synthesis employing fluoroform, which is an atom-economical, inexpensive, and most promising fluoromethylating reagent, remains undeveloped,[2,3] despite the explosive growth of synthetic fluorine chemistry involving the development of practical and reliable reactions and reagents.[4]

The selective introduction of the difluoromethyl (CF_2H) group into biologically active molecules is of particular interest in pharmaceuticals and agrochemicals because the group can bring about some useful effects, such as the enhancement of binding affinity, bioavailability, and lipophilicity.[5] Actually, the difluoromethyl group is known to act as a bioisostere of alcohols and thiols, which is a lipophilic hydrogen bond donor. Common syntheses of compounds containing the difluoromethyl group can be conducted via the deoxofluorination of aldehydes with SF_4, DAST (*N*,*N*-diethylaminosulfur trifluoride), and its derivatives as harsh reagents.[6] The nucleophilic, electrophilic, and radical difluoromethylations as an alternative approach have been developed for the direct preparation of compounds containing the difluoromethyl group;[5,7] however, the difluoromethylation on sp^3 carbon involving carbon−carbon bond formation has scarcely been reported.[2d,5,8] During our research project, Dolbier and co-workers reported a single example of α-difluoromethylation of nitrile with a large excess of fluoroform in the presence of KOH as a base to give only low yield (30%).[9] Herein, we present our α-difluoromethylation on sp^3 carbon of various nitrile compounds[10] using fluoroform in the presence of lithium base. The reaction is operationally simple and fast (completed in a few minutes); only treatment of fluoroform (1.5−2.0 equiv) and *n*-BuLi (1.1 equiv) to nitriles without transition metal or other additives leads to the valuable α-difluoromethylated products with a quaternary carbon center. Significantly, the Ruppert−Prakash reagent (CF_3TMS),[11] which is one of the most versatile and commercially available trifluoromethylating reagents, is also applicable to the reaction providing the α-siladifluoromethylated products,[12] which can be exploited for sequential carbon−carbon bond-forming reactions to transform into the compounds bearing the difluoromethylene ($-CF_2-$) group regarding as a bioisostere to ethereal oxygen.

We initiated our research by examining the reaction between fluoroform and 2,2-diphenylacetonitrile **1a** in the presence of lithium base as a model system to optimize the reaction conditions (Table 1). Initially, following addition of 1.0 or 0.9 equiv of *n*-BuLi to **1a** in THF, fluoroform (5.0 equiv) was bubbled into the solution at −78 °C. However, the reaction did not proceed at all, resulting in almost complete recovery of **1a** (entry 1). Significantly, employment of a slight excess of *n*-BuLi (1.1 equiv) was found to provide the desirable difluoromethylated product **2a** in excellent yield (entry 2). Increasing the amount of *n*-BuLi (2.0 equiv) did not cause a deleterious effect (entry 3). As briefly illustrated, various lithium bases, such as MeLi, LDA, LTMP, and LHMDS, were evaluated, and consequently, *n*-BuLi was demonstrated to be the most efficient lithium base (entries 2 vs 4−7). Surprisingly, the reaction was completed within 1 min even at −78 °C, using even 1.5 equiv of fluoroform (entry 10). THF was also found to be better solvent than other coordinating solvents for this reaction.

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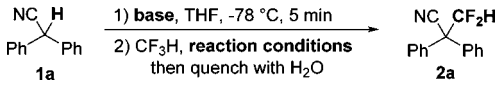
Table 1. α-Difluoromethylation with Fluoroform[a]

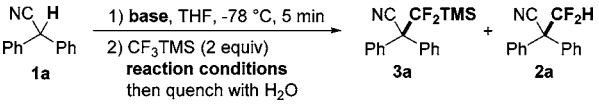


entry	base	reaction conditions	yield[b] (%)
1	*n*-BuLi (0.9 or 1.0 equiv)	CF_3H (5 equiv), −78 °C, 1 h	0
2	*n*-BuLi (1.1 equiv)	CF_3H (5 equiv), −78 °C, 1 h	98
3	*n*-BuLi (2.0 equiv)	CF_3H (5 equiv), −78 °C, 1 h	92
4	MeLi (1.1 equiv)	CF_3H (5 equiv), −78 °C, 1 h	96
5	LDA (1.1 equiv)	CF_3H (5 equiv), −78 °C, 1 h	0
6	LTMP (1.1 equiv)	CF_3H (5 equiv), −78 °C, 1 h	73
7	LHMDS (1.1 equiv)	CF_3H (5 equiv), −78 °C, 1 h	0
8	*n*-BuLi (1.1 equiv)	CF_3H (2 equiv), −78 °C, 1 h	95
9	*n*-BuLi (1.1 equiv)	CF_3H (2 equiv), −78 °C, 5 min	93
10	***n*-BuLi (1.1 equiv)**	**CF_3H (2 equiv), −78 °C, 1 min**	**96 (85)**[c]

[a]Conditions: After addition of lithium base to **1a** in THF, CF_3H was bubbled to the mixture at −78 °C. The reaction was quenched with H_2O. [b]Yields were determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard. [c]1.5 equiv of CF_3H was used.

We next envisioned that this strategy would be adaptable to α-siladifluoromethylation using the Ruppert−Prakash reagent (CF_3TMS) in lieu of fluoroform as a difluoromethyl source (Table 2). Similarly, no desired product was detected with 1.0 or

Table 2. α-Siladifluoromethylation with Ruppert−Prakash Reagent[a]



entry	base	reaction conditions	3a/2a of yield[b] (%)
1	*n*-BuLi (0.9 or 1.0 equiv)	−78 °C, 1 h	0/<1
2	***n*-BuLi (1.1 equiv)**	**−78 °C, 10 min**	**0/87**
3	*n*-BuLi (1.1 equiv)	−78 °C, 1 h	29/54
4	*n*-BuLi (1.1 equiv)	−40 °C, 1 h	86/2
5	*n*-BuLi (1.1 equiv)	−20 °C, 1 h	90/2
6	***n*-BuLi (1.1 equiv)**	**rt, 10 min**	**90/0**

[a]Conditions: After addition of base to **1a** in THF, CF_3TMS (2 equiv) was added to the mixture at −78 °C. The reaction was quenched with H_2O. [b)]Yields were determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard.

0.9 equiv of *n*-BuLi (entry 1). As expected, in the presence of 1.1 equiv of *n*-BuLi, the reaction of **1a** with CF_3TMS (2.0 equiv) took place smoothly within 10 min but, however, did not provide the desired α-siladifluoromethylated product **3a** but instead the α-difluoromethylated counterpart **2a** selectively in 87% yield (entry 2). Importantly, in the prolonged reaction time at −78 °C, the mixtures of **2a** and **3a** were formed in totally 83% yield (entry 3). The elevated reaction temperature (−40 and −20 °C) led to the almost single product **3a** in 86% and 90% yields, respectively (entries 4 and 5). These results imply that the reaction was completed at −78 °C within 10 min, generating in situ the reaction intermediate **7** which can be transformed to both **2a** and **3a** under the different reaction conditions (*vide infra*: Scheme 2). Finally, the reaction was found to be completed at room temperature within 10 min, providing only single product **3a** in 90% yield (entry 6).

Having identified the optimal conditions of both the α-difluoromethylation and α-siladifluoromethylation, we turned our attention to evaluate the generality of these protocols (Figure 1). High yields were generally observed for 2,2-diarylacetonitrile

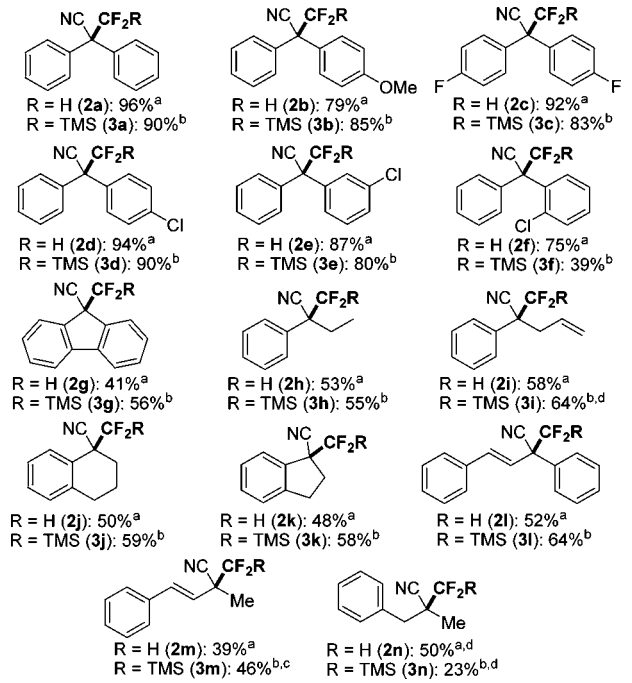


Figure 1. Substrate scope and functional group tolerance. Yields were determined by ^{19}F NMR analysis using benzotrifluoride as an internal standard. (a) Method A: After addition of *n*-BuLi (0.55 mmol) to **1** (0.5 mmol) in THF (1.0 mL) at −78 °C, CF_3H (1.0 mmol) was added at −78 °C, and the mixture was stirred for 1−5 min at −78 °C. (b) Method B: After addition of *n*-BuLi (0.55 mmol) to **1** (0.5 mmol) in THF (1.0 mL) at −78 °C, CF_3TMS (1.0 mmol) was added at −78 °C, and the mixture was stirred for 1 h at room temperature. (c) *n*-BuLi (1.0 mmol) was used. (d) LTMP (1.0 mmol) instead of *n*-BuLi was used.

1b−d bearing not only electron-donating but also -withdrawing substituents on the *para*-position. 2,2-Diarylacetonitrile **1d−f** with a chlorine substituent, regardless of the arene substitution position (*para*-, *meta*-, and *ortho*-), could be converted to the corresponding product, while a decrease in yield was observed with *ortho*-substituted **1f**. Nitrile **1g** with a fluorene backbone was also compatible with these reactions. As encouraged, not only acyclic but also cyclic α-monoalkylated nitriles **1h−k** were applicable to these reactions, while yields were moderate, respectively. The reactions of substrates **1l−m** with the vinylic substituent also occurred, resulting in the formation of the desired α-(sila)difluoromethylated products, but along with the γ-(sila)difluoromethylated byproducts in about 20% yields. Even aliphatic nitrile **1n** was allowed to react with CF_3H and CF_3TMS by treatment of LTMP instead of *n*-BuLi, which reacted with **1n** to form *n*-BuLi adduct, providing the corresponding products **2n** and **3n**, respectively.

The mechanisms of reactions with fluoroform and the Ruppert−Prakash reagent was researched experimentally (Scheme 1). At first, combination of **1a** and *n*-BuLi (1.0 equiv) in THF followed by quench with D_2O resulted in the formation of α-deuterated **1a-D** (>95% D incorporation) quantitatively without byproduct, while avoiding the addition reaction of *n*-BuLi to the cyano group (eq 1). The reaction of **1a** with fluoroform under the optimized reaction conditions followed by

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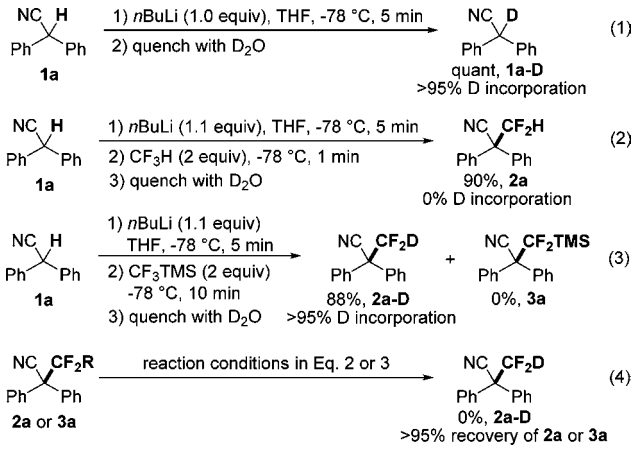
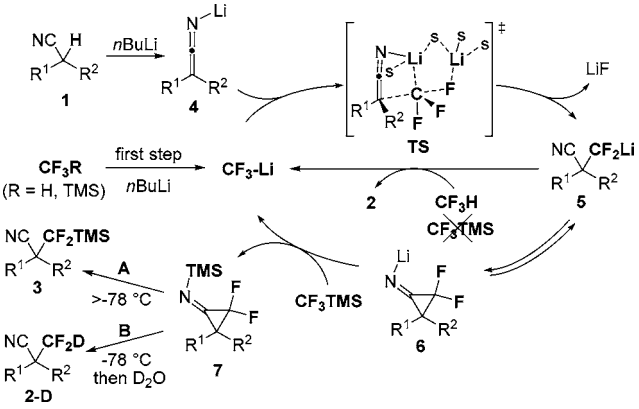
Scheme 1. Experiments for Consideration of Reaction Mechanism



quench with D_2O did not afford deuterated **2a-D** but **2a** in 90% yield (eq 2). In sharp contrast to the fluoroform system, the reaction with the Ruppert−Prakash reagent at −78 °C for 10 min followed by quench with D_2O, and only difluoromethylated **2a-D** was obtained in 88% yield without the formation of **3a** (eq 3). It was also found that each product **2a** and **3a** underwent no H-D and TMS-D exchange under each reaction conditions shown in eqs 2 and 3, respectively (eq 4).

On the basis of these observations and DFT calculations, mechanisms in difluoromethylation are visualized in Scheme 2.

Scheme 2. Plausible Mechanism of α-Difluoromethylation



In the case of fluoroform (CF_3R, R = H), the remaining *n*-BuLi deprotonates fluoroform to give lithium carbenoid (CF_3Li).[1b,13] Subsequently, lithium carbenoid is allowed to react with lithium ketene imine **4**, which can be quantitatively generated by combination of nitrile **1** and *n*-BuLi,[14] leading eventually to difluoroalkyllithium **5** via the proposed **TS**.[15,16] Difluoromethyllithium **5** is more basic than **4** and can abstract a proton of fluoroform to provide protonated product **2** without **2a-D** formation even by D_2O quench (Scheme 1, eq 2). Similar to mechanistic studies of the direct difluoromethylation of lithium enolate and lithium carbenoid (CF_3Li),[15] the transition state was found to be likely **TS** via the bimetallic carbenoid with dual activation of the lithium nonbutterfly-shaped carbenoid (Figure 2). The lithium carbenoid rather than free difluorocarbene reacts with **4** in S_N2-type displacement via the angle obtuse enough ($C^1-C^2-F^1$: 167.0°) by the activation of C−F bond (C^2-F^1: 2.06 Å; C^2-F^2, C^2-F^3: 1.34 Å; C^1-C^2: 3.25 Å) with Li−F association.

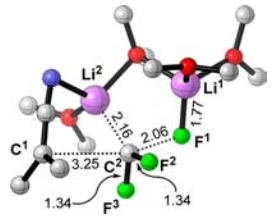
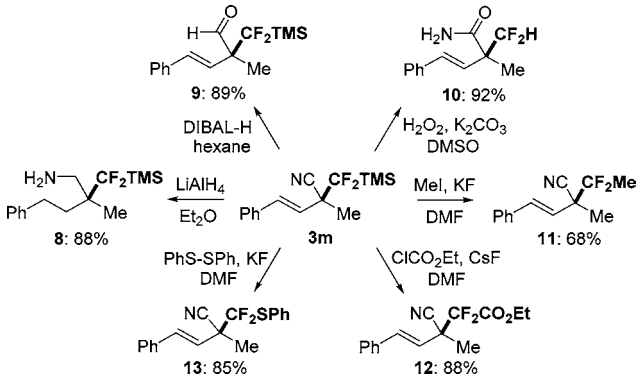


Figure 2. Transition state **TS** was computed at the B3LYP-D3/6-31+G*/IEF-PCM level of theory in THF. Distances in Å. R_1, R_2 = Me, s = Me_2O in **TS** of Scheme 2. Unimportant hydrogen atoms are omitted.

In the case of the Ruppert−Prakash reagent (CF_3R, R = TMS), difluoromethyllithium **5** is also formed via the **TS**. However, **5** would afford not directly silylated **3** but also difluorocyclopropane **6**, and eventually silylated **7**, due to steric demand around the all-carbon quaternary center in **5**. In fact, the corresponding peak (δ_F: −125)[17] of **7** was observed in ^{19}F NMR analysis at temperatures lower than −60 °C. Intramolecular transfer of the silyl group in **7** or intermolecular reaction of **7** with CF_3TMS at temperatures higher than −78 °C (conditions **A**) selectively led to α-siladifluoromethylated product **3** (Table 2, entries 2 vs 3−6). On the other hand, difluoromethylated product **2**(**-D**) is selectively obtained at lower temperature (conditions **B**: −78 °C, less than 10 min), as actually deuterated by D_2O quench (Scheme 1, eq 3).

With these successes in terms of the wide scope of nitriles, we transformed the α-siladifluoromethylated product into valuable compounds bearing various functional groups (Scheme 3). The

Scheme 3. Applications to Transforming Reactions



reductions of **3m** in the presence of $LiAlH_4$ or DIBAL-H provided amine **8** and aldehyde **9**, respectively, maintaining the trimethylsilyl group. The oxidation of **3m** using H_2O_2 and K_2CO_3 led to amide **10**, while protodesilylation occurred. The methylation and esterification using MeI and ethyl chloroformate as electrophiles proceeded smoothly by virtue of the reactive silyl functionality, providing the fluoroalkylated products **11** and **12**, respectively. Moreover, **3m** possessing a quaternary carbon center was converted to the corresponding thioether **13** with disulfide using spray dry potassium fluoride.

In summary, we have succeeded in the α-difluoromethylation on the sp^3 carbon of various nitrile compounds with a slight excess amount of *n*-BuLi (1.1 equiv) and fluoroform (2.0 equiv), which is an ideal fluoromethylating reagent, to provide the corresponding α-difluoromethylated products with quaternary carbon center in moderate to high yields. The reaction is

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completed within 1 min and operationally simple without transition-metal and other additives. The Ruppert−Prakash reagent is also applicable to the reaction to selectively provide the α-siladifluoromethylated and α-difluoromethylated products depending on the reaction temperature. Development of valuable and novel catalytic difluoromethylations using fluoroform and the Ruppert−Prakash reagent 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.5b02438.

Experimental procedures and compound characterization data (PDF)
X-ray crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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