(Sila)Difluoromethylation of Fluorenyllithium with CF$_3$H and CF$_3$TMS

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Dedicated to Professor V. Snieckus on the occasion of his 80th birthday.

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Abstract Difluoromethylation of the C9-H site of the fluorene ring using lithium base and fluoroform (CF$_3$H), which is one of the most cost-effective difluoromethylating reagents, is attained to give difluoromethylated fluorenes with an all-carbon quaternary center. The Ruppert–Prakash reagent (CF$_3$TMS) can also be applied to the present reaction system, providing siladifluoromethylated fluorenes that can be utilized for sequential carbon–carbon bond-forming reactions through activation of the silyl group.

Key words fluoroform, Ruppert–Prakash reagent, bioisostere, fluorene, difluoromethylation, difluoroethylenyl, difluorocarbene

Enormous numbers of synthetic organofluorine compounds have been widely utilized in various fields such as bioorganic chemistry, medicinal chemistry, and material science, in sharp contrast to only twelve known natural organofluorine compounds.$^1$ Particularly high demand for chiral and achiral trifluoromethylated compounds has remarkably expanded the methodologies available for trifluoromethylation given that the pharmaceutical and agrochemical industries commonly utilize trifluoromethylated compounds.$^2$ Quite recently, the difluoromethyl (CF$_2$H) and difluoroethylenyl (CF$_3$CR) groups have attracted much attention, since these difluoro compounds are considered as bioisosteres$^3$ of alcohol/thiol and ether functional groups, respectively. Furthermore, difluoromethyl(ene) groups increase metabolic stability and lipophilicity.$^4$ To synthesize difluoromethylated and difluoroethylenylated compounds, deoxofluorination of aldehydes and ketones has been employed.$^5$ On the other hand, the development of direct introduction of the CF$_2$H and CF$_3$R groups via a carbon–carbon bond-forming reaction is central to future developments in the area of difluoro-compounds.$^4$ For instance, much attention has been paid to elaboration in metal-catalyzed or metal-mediated cross-coupling reactions, affording difluoromethylated and difluoroethylenylated arenes.$^4e,4g–h,6$

Fluoroform (CF$_3$H, HFC-23), produced in large amounts as a by-product of Teflon® (DuPont) manufacturing, is low cost and hence a cost-effective fluoromethyl source.$^7$ Accordingly, various types of trifluoromethylations with fluoroform as a trifluoromethyl source have been reported.$^8$ In sharp contrast, we have already described the difluoromethylations of carbonyl compounds, nitriles, and terminal alkynes by combination of lithium base and fluoroform as a difluoromethyl source involving ’Umpolung’. Herein, we report the difluoromethylation of the C9-H site of the fluorene ring through generation of fluorenyllithium. Significantly, the synthetic method can be expanded to siladifluoromethylation$^9b,9e,11$ of fluorenes using the silylated version of fluoroform, namely the Ruppert–Prakash reagent (CF$_3$TMS), which is also employed as a trifluoromethylating anion source.$^{12}$

Difluoromethylation of the C9-H site of fluorene ring was explored under basic reaction conditions (Table 1).$^9$ Initially, following addition of nBuLi (1.1 equiv) to fluorene 1a in tetrahydrofuran (THF), fluoroform (2.0 equiv) was bubbled into the solution at –78 °C, providing the corresponding difluoromethylated product 2a in 23% yield after just 5 min (entry 1). An increase in yield (44%) was observed by prolonging the reaction time to 1 h (entry 2). Additional nBuLi (2.0 equiv) did not bring about a marked improvement, giving the desired product 2a in 46% and 50% yields after 5 min and 1 hour, respectively (entries 3 and 4). Various lithium bases, such as MeLi, LDA, and LHMDS, and LTMP were also employed under the same reaction conditions but resulted in lower yields.$^{9b}$
A variety of fluorenyllithiums generated using nBuLi were reacted with fluoroform (Figure 1). Fluorenes 1b–d, bearing alkyl groups such as t-butyl, n-hexyl, and methyl on the C9 site of the fluorene ring, underwent reaction to give the corresponding products 2b–d. Unfortunately, difluoromethylation of nonsubstituted fluorene 1e failed, despite extensive variation of reaction conditions (Methods A–C). In sharp contrast, fluorenes 1f and 1g, possessing electron-withdrawing substituents such as ester and cyano groups, were found to be compatible with the conditions, leading to products 2f and 2g in 63 and 73% yields, respectively. In addition, the reaction of fluorene 1h, bearing a trimethylsilyl group, occurred with fluoroform, but formation of fluoroolefin 3 was observed as a result of β-F elimination (Scheme 1).

**Table 1** Difluoromethylation with Fluoroform

| Entry | X (equiv) | Reaction conditions | Yield of 2a (%)<sup>a</sup> |
|-------|----------|---------------------|-----------------------------|
| 1     | 1.1      | –78 °C, 5 min       | 23                          |
| 2     | 1.1      | –78 °C, 1 h         | 44                          |
| 3     | 2.0      | –78 °C, 5 min       | 46                          |
| 4     | 2.0      | –78 °C, 1 h         | 50                          |

<sup>a</sup> Yields were determined by <sup>19</sup>F NMR analysis using benzotrifluoride (BTF) as internal standard.

Subsequently, we focused on the siladifluoromethylation of fluorenes with the silylated version (CF<sub>3</sub>TMS) of fluoroform (Table 2). As expected, the reaction of fluorene 1a with CF<sub>3</sub>TMS (2.0 equiv) in the presence of nBuLi (1.1 equiv) proceeded at –78 °C, but the yield of siladifluoromethylated product 4a was low (entry 1). Importantly, the yield was markedly improved up to 83% yield by warming to room temperature (entry 2). Employment of 2 equiv of nBuLi was also found to lead to high (84%) yields of 4a even at –78 °C within 5 min (entry 3), while the elevated temperature slightly lowered the yield under these conditions (entry 4).

**Table 2** Difluoromethylation with the Ruppert–Prakash reagent

| Entry | X (equiv) | Reaction conditions | Yield of 4a (%)<sup>a</sup> |
|-------|----------|---------------------|-----------------------------|
| 1     | 1.1      | –78 °C, 5 min       | 8                           |
| 2     | 1.1      | –78 °C, 1 h         | 83                          |
| 3     | 2.0      | –78 °C, 5 min       | 84                          |
| 4     | 2.0      | –78 °C, 1 h         | 71                          |

<sup>a</sup> Yields were determined by <sup>19</sup>F NMR analysis using benzotrifluoride (BTF) as internal standard.

The substrate scope in the siladifluoromethylation was also investigated (Figure 2). Although the reaction of 1b, bearing the sterically more demanding t-butyl group, gave a low yield of 4b, fluorenes 1c and 1d, with hexyl and methyl groups, smoothly underwent reaction to furnish the corresponding products 4c and 4d in 71% and 79% yields, respectively. We were delighted to find that siladifluoromethylation took place with nonsubstituted fluorene 1e on modification of the reaction conditions (Method C: nBuLi (1.1 equiv), –78 °C, 1 h), resulting in 80% yield of product 4e.
The siladifluoromethylated fluorine products can be employed for sequential carbon–carbon bond-forming reactions to give ‘semi-fluoroalkyl’ fluorenes of material importance.15 As shown in Scheme 2, the reaction of siladifluoromethyl adduct \( \text{4c} \) with \( \text{MeI} \) (5.0 equiv) in the presence of tetrabutylammonium fluoride (TBAF) (1.0 equiv) was found to give the corresponding methylated product \( \text{5c} \).

The present (sila)difluoromethylation reaction is critically \( pK_a \) dependent (Figure 3). The reaction proceeds with acidic and less nucleophilic esters and nitriles of low \( pK_a \) values (Group A) to provide the products \( \text{4f} \) and \( \text{4g} \). Enolates\(^\text{5a}\) and acetylides\(^\text{5d}\) with \( pK_a \) values comparable to that of fluoroform (Group B) efficiently produce the (sila)difluoromethyl products with not only fluoroform but also the silyl derivative (CF\(_3\)TMS). Additionally, basic compounds such as arenes with higher \( pK_a \) values than fluoroform (Group C) eventually deprotonate fluoroform through directed ortho-metalation [DOM].\(^\text{16}\) Therefore, the CF\(_3\)Si derivatives have to be employed for siladifluoromethylation of arenes. In a similar manner, indene \( \text{1i} \) was also a substrate for siladifluoromethylation with the Ruppert–Prakash reagent (CF\(_3\)TMS) to provide the corresponding product \( \text{4i} \) (Scheme 3).\(^\text{3}\)

Experiments to clarify the reaction mechanisms were conducted using fluoroform and the Ruppert–Prakash reagent (Scheme 4). The addition of \( \text{nBuLi (1.1 equiv)} \) to fluorene \( \text{1a} \) in THF followed by quenching with D\(_2\)O gave \( \alpha \)-deuterated \( \text{1a-D} \) (\( >95\% \) D incorporation) quantitatively to prove the complete generation of fluorenyllithium (Eq. 1). However, reactions of \( \text{1a} \) with not only fluoroform but also the Ruppert–Prakash reagent in the presence of \( \text{nBuLi} \) provided no deuterated \( \text{2a-D} \) or \( \text{4a-D} \) (Eq. 2 and 3). Even employing...
only 0.9 equiv of nBuLi, fluorene 1a underwent the difluoromethylation reaction (Eq. 4). These results indicate that fluorenyllithium prepared from 1a can deprotonate fluoroform to generate the lithium carbenoid (CF3Li) as an active species for (sila)difluoromethylation.9b,9c

On the basis of these observations and our DFT/AFIR calculations on carbonyl and nitrile systems,9b,9c the mechanisms in the difluoromethylation and siladifluoromethylation of fluorenes could be proposed (Scheme 5).9b–d Initially, the remaining nBuLi or fluorenyllithium (Fl-Li) can deprotonate the fluoroform or activate the Ruppert–Prakash reagent to generate lithium carbenoid (CF3Li). Upon generation of the lithium carbenoid, the reaction can produce fluorenyldifluoromethyl lithium species (Fl-CF2Li) via an S_N2-type process9c in the bimetallic Fl-Li/CF3Li complex (5). Finally, the difluoromethyl lithium species, which possesses higher basicity and nucleophilicity than fluorenyllithium (Fl-Li), can react with fluoroform or its silylated analogue to give the products 2 or 4, and simultaneously regenerate the lithium carbenoid.

In conclusion, we have succeeded in (sila)difluoromethylation at C9-H of the fluorene ring (1) with nBuLi and fluoroform (CF3H) or the silylated analogue (CF3TMS), giving (sila)difluoromethylated fluorenes with an all-carbon quaternary center (Table 3). This synthetic method is operationally simple, employing fluorene substrates, a lithium base, and (silylated) fluoroform without need for transition-metals or other additives. The reaction affords the (sila)difluoromethylated fluorenes leading eventually to ‘semi-fluoroalkyl’ fluorenes via sequential carbon–carbon bond-forming reactions.

Table 3 (Siladifluoromethylation at C9-H of the Fluorene Ring of 1

| Entry | R         | HCF3 yield (%) | MeSiCF3 (%) |
|-------|-----------|----------------|-------------|
| 1     | Ph (a)    | 56a            | 84a         |
| 2     | t-Bu (b)  | 22a            | 14a         |
| 3     | n-Hex (c) | 31b            | 71b         |
| 4     | Me (d)    | 33b            | 79b         |
| 5     | H (e)     | 0              | 82c         |
| 6     | CO2Me (f) | 63a            | 97b         |
| 7     | CN (g)    | 73a            | 56b         |
| 8     | SiMe3 (h) | (39)a          | 15          |
| 9     | indene (l) |              | 32c         |

*a Method A.  
*b Method B.  
*c Method C.

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Supporting Information

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