

(Sila)Difluoromethylation of Fluorenyllithium with CF₃H and CF₃TMS

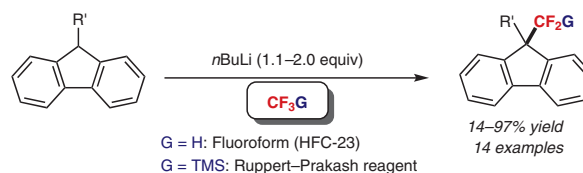
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Dedicated to Professor V. Snieckus on the occasion of his 80th birthday.



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Abstract Difluoromethylation of the C9-H site of the fluorene ring using lithium base and fluoroform (CF₃H), 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 (CF₃TMS) 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.

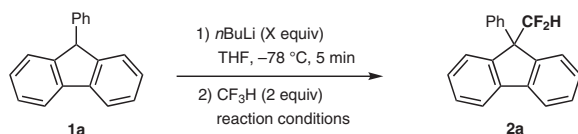
Key words fluoroform, Ruppert–Prakash reagent, bioisostere, fluorene, difluoromethylation, difluoromethyl, difluoromethylene, difluorocarbene

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 (CF₂H) and difluoromethylene (CF₂R) groups have attracted much attention, since these difluoro compounds are considered as bioisosteres³ of alcohol/thiol and ether functional groups, respectively. Furthermore, difluoromethyl(ene) groups increase metabolic stability and lipophilicity.⁴ To synthesize difluoromethylated and difluoromethylenated compounds, deoxofluorination of aldehydes and ketones has been employed.⁵ On the other hand, the development of direct introduction of the CF₂H and CF₂R 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 difluoromethylenated arenes.^{4e,4g–h,6}

Fluoroform (CF₃H, 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’.^{9,10} 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 (CF₃TMS), 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 *n*BuLi (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 *n*BuLi (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}

Table 1 Difluoromethylation with Fluoroform¹³

Entry	X (equiv)	Reaction conditions	Yield of 2a (%) ^a
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

^a Yields were determined by ¹⁹F NMR analysis using benzotrifluoride (BTF) as internal standard.

A variety of fluorenyllithiums generated using *n*BuLi 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**^{9b} 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).

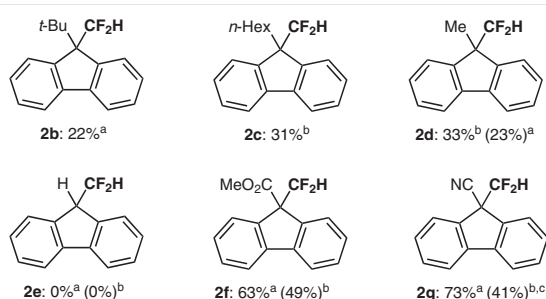
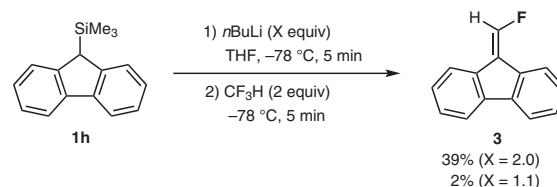
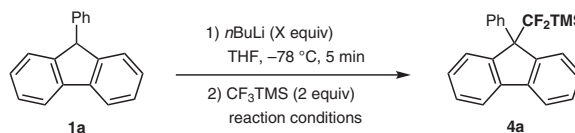


Figure 1 Substrate scope in difluoromethylation. Yields were determined by ¹⁹F NMR analysis using benzotrifluoride (BTF) as internal standard. ^a Method A: *n*BuLi (0.2 mmol), **1** (0.1 mmol), and CF₃H (0.2 mmol) in THF (1 mL), 5 min, –78 °C. ^b Method B: *n*BuLi (0.11 mmol), **1** (0.1 mmol), and CF₃H (0.2 mmol) in THF (1 mL) for 1 h at –78 °C. ^c Reaction time 5 min.

**Scheme 1** Production of fluoroolefin **3**

Subsequently, we focused on the siladifluoromethylation of fluorenes with the silylated version (CF₃TMS) of fluoroform (Table 2). As expected, the reaction of fluorene **1a** with CF₃TMS (2.0 equiv) in the presence of *n*BuLi (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 *n*BuLi 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 reagent¹⁴

Entry	X (equiv)	Reaction conditions	Yield of 4a (%) ^a
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

^a Yields were determined by ¹⁹F 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: *n*BuLi (1.1 equiv), –78 °C, 1 h), resulting in 80% yield of product **4e**.

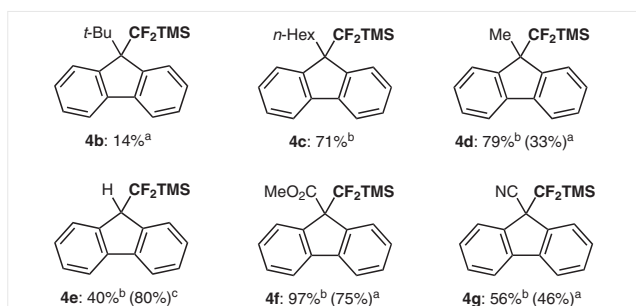
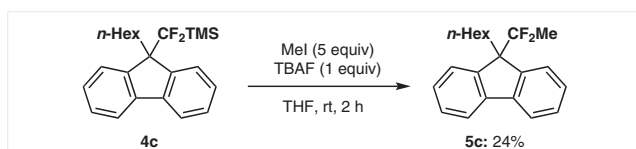


Figure 2 Substrate scope in siladifluoromethylation. Yields were determined by ^{19}F NMR using benzotrifluoride (BTF) as an internal standard. ^a Method A: *n*BuLi (0.2 mmol), **1** (0.1 mmol), and CF_3TMS (0.2 mmol) in THF (1 mL), 5 min, -78°C ; ^b Method B: *n*BuLi (0.11 mmol), **1** (0.1 mmol), and CF_3TMS (0.2 mmol) in THF (1 mL), 1 h, r.t.; ^c Method C: *n*BuLi (0.11 mmol), **1** (0.1 mmol), and CF_3TMS (0.2 mmol) in THF (1 mL), 1 h, -78°C .

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 **4c** with MeI (5.0 equiv) in the presence of tetrabutylammonium fluoride (TBAF) (1.0 equiv) was found to give the corresponding methylated product **5c**.



Scheme 2 Methylation of trimethylsilyldifluoromethyl group. Yields were determined by ^{19}F NMR using benzotrifluoride (BTF) as internal standard.

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 **4f** and **4g**. Enolates^{9a} and acetylides^{9d} 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_3TMS). Additionally, basic compounds such as arenes with higher pK_a values than fluoroform (Group C) eventually deprotonate fluoroform through directed *ortho*-metalation [DOM].¹⁶ Therefore, the CF_3Si derivatives have to be employed for siladifluoromethylation of arenes. In a similar manner, indene **1i** was also a substrate for siladifluoromethylation with the Ruppert–Prakash reagent (CF_3TMS) to provide the corresponding product **4i** (Scheme 3).

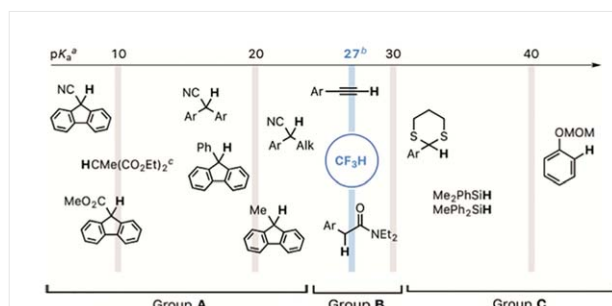
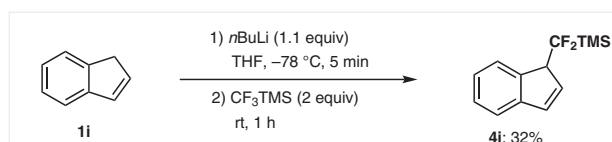
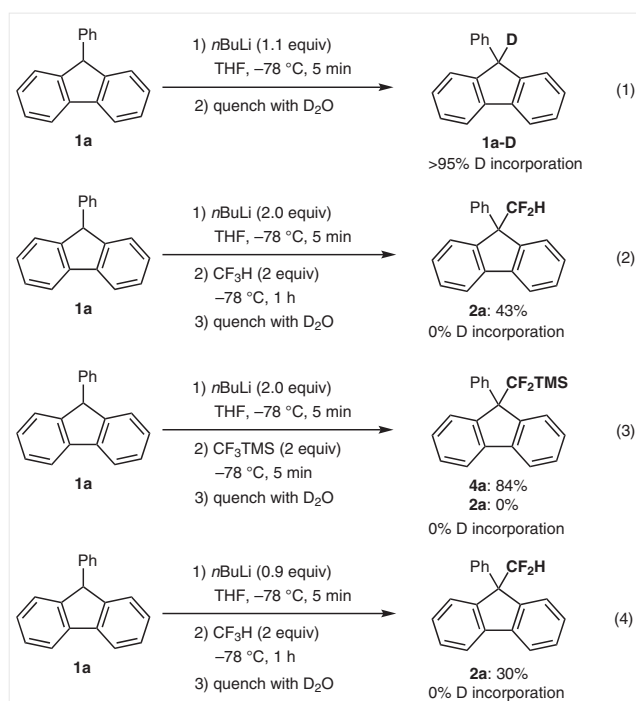


Figure 3 Classification of Substrates. ^a Values in dimethylsulfoxide.¹⁶ ^b Values in H_2O .¹⁷



Scheme 3 Siladifluoromethylation of indene

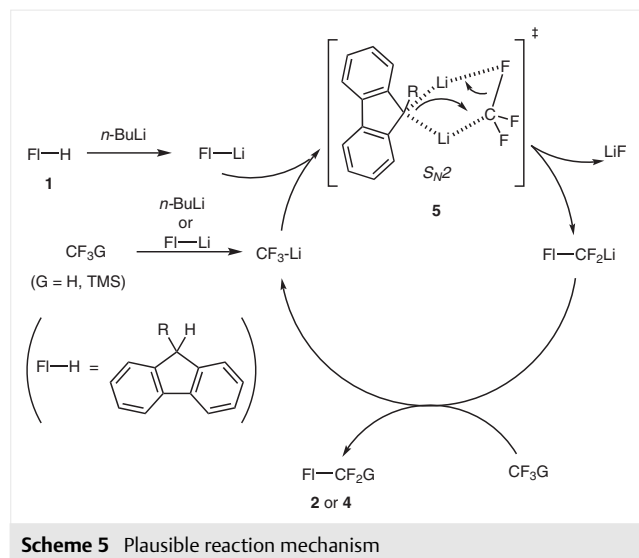
Experiments to clarify the reaction mechanisms were conducted using fluoroform and the Ruppert–Prakash reagent (Scheme 4). The addition of *n*BuLi (1.1 equiv) to fluorene **1a** in THF followed by quenching with D_2O gave α -deuterated **1a-D** (>95% D incorporation) quantitatively to prove the complete generation of fluorenyllithium (Eq. 1). However, reactions of **1a** with not only fluoroform but also the Ruppert–Prakash reagent in the presence of *n*BuLi provided no deuterated **2a-D** or **4a-D** (Eq. 2 and 3). Even employing



Scheme 4 Experiments for elucidating the reaction mechanism

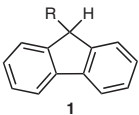
only 0.9 equiv of *n*BuLi, fluorene **1a** underwent the difluoromethylation reaction (Eq. 4). These results indicate that fluorenyllithium prepared from **1a** can deprotonate fluoroform to generate the lithium carbenoid (CF₃Li) as an active species for (sila)difluoromethylation.^{9b}

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 *n*BuLi 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 process^{9c} 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 *n*BuLi 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 (Sila)difluoromethylation at C9-H of the Fluorene Ring of **1**



Entry	R	HCF ₃ yield (%)	MeSiCF ₃ (%)
1	Ph (a)	56 ^a	84 ^a
2	<i>t</i> -Bu (b)	22 ^a	14 ^a
3	<i>n</i> -Hex (c)	31 ^b	71 ^b
4	Me (d)	33 ^b	79 ^b
5	H (e)	0	82 ^c
6	CO ₂ Me (f)	63 ^a	97 ^b
7	CN (g)	73 ^a	56 ^b
8	SiMe ₃ (h)	(39) ^a	15
9	indene (i)	–	32 ^c

^a Method A.

^b Method B.

^c Method C.

Funding Information

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Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0037-1610361>.

References and Notes

- (a) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (b) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359. (c) Ojima, I. *Fluorine in Medicinal Chemistry and Chemical Biology*; Wiley-Blackwell: Chichester U. K., **2009**. (d) Xing, L.; Blakemore, D. C.; Narayanan, A.; Unwalla, R.; Lovering, F.; Denny, R. A.; Zhou, H.; Bunnage, M. E. *ChemMedChem* **2015**, *10*, 715. (e) O'Hagan, D.; Deng, H. *Chem. Rev.* **2015**, *115*, 634. (f) Tirotta, I.; Dichiarante, V.; Pigliacelli, C.; Cavallo, G.; Terraneo, G.; Bombelli, F. B.; Metrangolo, P.; Resnati, G. *Chem. Rev.* **2015**, *115*, 1106.
- (2) For reviews, see: (a) Charpentier, J.; Fruh, N.; Togni, A. *Chem. Rev.* **2015**, *115*, 650. (b) Yang, X.; Wu, T.; Phipps, R. J.; Toste, F. D. *Chem. Rev.* **2015**, *115*, 826. (c) Sugiishi, T.; Amii, H.; Aikawa, K.; Mikami, K. *Beilstein J. Org. Chem.* **2015**, *11*, 2661. (d) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214. (e) Tomashenko, O. A.; Grushin, V. V. *Chem. Rev.* **2011**, *111*, 4475. (f) Nie, J.; Guo, H.-C.; Cahard, D.; Ma, J.-A. *Chem. Rev.* **2011**, *111*, 455.
- (3) (a) Zafrani, Y.; Yeffet, D.; Sod-Moriah, G.; Berliner, A.; Amir, D.; Marciano, D.; Gershonov, E.; Saphier, S. *J. Med. Chem.* **2017**, *60*, 797. (b) Sessler, C. D.; Rahm, M.; Becker, S.; Goldberg, J. M. Wang F.; Lippard, S. J. *J. Am. Chem. Soc.* **2017**, *139*, 9325.

- (4) For reviews, see: (a) Hu, J.; Wang, F. *Chem. Commun.* **2009**, 7465. (b) Hu, J. *J. Fluorine Chem.* **2009**, 130, 1130. (c) Liu, Y.-L.; Yu, J.-S.; Zhou, J. *Asian J. Org. Chem.* **2013**, 2, 194. (d) Ni, C.; Hu, J. *Synthesis* **2014**, 46, 842. (e) Chen, B.; Vicic, D. *Top. Organomet. Chem.* **2014**, 52, 113. (f) Ni, C.; Hu, M.; Hu, J. *Chem. Rev.* **2015**, 115, 765. (g) Belhomme, M.-C.; Besset, T.; Poisson, T.; Pannecoucke, X. *Chem. Eur. J.* **2015**, 21, 12836. (h) Rong, J.; Ni, C.; Hu, J. *Asian J. Org. Chem.* **2017**, 6, 139.
- (5) (a) Singh, R. P.; Shreeve, J. M. *Synthesis* **2002**, 2561. (b) Kirk, K. L. *Org. Process Res. Dev.* **2008**, 12, 305. (c) Umemoto, T.; Singh, R. P.; Xu, Y.; Saito, N. *J. Am. Chem. Soc.* **2010**, 132, 18199. (d) Fujimoto, T.; Becker, F.; Ritter, T. *Org. Process Res. Dev.* **2014**, 18, 1041.
- (6) Selected reports for metal-mediated or -catalyzed difluoromethylations of aryl halides, see: (a) Fujikawa, K.; Fujioka, Y.; Kobayashi, A.; Amii, H. *Org. Lett.* **2011**, 13, 5560. (b) Fier, P. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, 134, 5524. (c) Prakash, G. K. S.; Ganesh, S. K.; Jones, J.-P.; Kulkarni, A.; Masood, K.; Swabeck, J. K.; Olah, G. A. *Angew. Chem. Int. Ed.* **2012**, 51, 12090. (d) Gu, Y.; Leng, X.-B.; Shen, Q. *Nat. Commun.* **2014**, 5, 5405. (e) Xu, L.; Vicic, D. A. *J. Am. Chem. Soc.* **2016**, 138, 2536. (f) Serizawa, H.; Ishii, K.; Aikawa, K.; Mikami, K. *Org. Lett.* **2016**, 18, 3686. (g) Aikawa, A.; Serizawa, H.; Ishii, K.; Mikami, K. *Org. Lett.* **2016**, 18, 3690. (h) Bour, J. R.; Kariofillis, S. K.; Sanford, M. S. *Organometallics* **2017**, 36, 1220. (i) Lu, C.; Gu, Y.; Wu, J.; Gu, Y.; Shen, Q. *Chem. Sci.* **2017**, 8, 4848.
- (7) For reviews, see: (a) Han, W.; Haodong, Y. L.; Tang, H.; Liu, H. *J. Fluorine Chem.* **2012**, 140, 7. (b) Zhang, C. *ARKIVOC* **2017**, 67.
- (8) (a) Shono, T.; Ishifune, M.; Okada, T.; Kashimura, S. *J. Org. Chem.* **1991**, 56, 2. (b) Barhdadi, R.; Troupel, M.; Périchon, J. *Chem. Commun.* **1998**, 1251. (c) Folléas, B.; Marek, I.; Normant, J.-F.; Saint-Jalmes, L. *Tetrahedron Lett.* **1998**, 39, 2973. (d) Russell, J.; Roques, N. *Tetrahedron* **1998**, 54, 13771. (e) Folléas, B.; Marek, I.; Normant, J.-F.; Saint-Jalmes, L. *Tetrahedron* **2000**, 56, 275. (f) Large, S.; Roques, N.; Langlois, B. R. *J. Org. Chem.* **2000**, 65, 8848. (g) Billard, T.; Bruns, S.; Langlois, B. R. *Org. Lett.* **2000**, 2, 2101. (h) Langlois, B. R.; Billard, T. *Synthesis* **2003**, 185. (i) Langlois, B. R.; Billard, T. *ACS Symp. Ser.* **2005**, 911, 57. (j) Popov, I.; Lindeman, S.; Daugulis, O. *J. Am. Chem. Soc.* **2011**, 133, 9286. (k) Zanardi, A.; Novikov, M. A.; Martin, E.; Benet-Buchholz, J.; Grushin, V. V. *J. Am. Chem. Soc.* **2011**, 133, 20901. (l) Prakash, G. K. S.; Jog, P. V.; Batamack, P. T. D.; Olah, G. A. *Science* **2012**, 338, 1324. (m) Novák, P.; Lishchynskiy, A.; Grushin, V. V. *Angew. Chem. Int. Ed.* **2012**, 51, 7767. (n) Kawai, H.; Yuan, Z.; Tokunaga, E.; Shibata, N. *Org. Biomol. Chem.* **2013**, 11, 1446. (o) Takemoto, S.; Grushin, V. V. *J. Am. Chem. Soc.* **2013**, 135, 16837. (p) Zhang, Y.; Fujii, M.; Serizawa, H.; Mikami, K. *J. Fluorine Chem.* **2013**, 156, 367. (q) van der Born, D.; Herscheid, J. D. M.; Orru, R. V. A.; Vugts, D. J. *Chem. Commun.* **2013**, 4018. (r) Lishchynskiy, A.; Novikov, M. A.; Martin, E.; Escudero-Adán, E. C.; Novák, P.; Grushin, V. V. *J. Org. Chem.* **2013**, 78, 11126. (s) Miloserdov, F. M.; Grushin, V. V. *J. Fluorine Chem.* **2014**, 167, 105. (t) Mazloomi, Z.; Bansode, A.; Benavente, P.; Lishchynskiy, A.; Urakawa, A.; Grushin, V. V. *Org. Process Res. Dev.* **2014**, 18, 1020. (u) Kononov, A. I.; Lishchynskiy, A.; Grushin, V. V. *J. Am. Chem. Soc.* **2014**, 136, 13410. (v) Lishchynskiy, A.; Berthon, G.; Grushin, V. V. *Chem. Commun.* **2014**, 10237. (w) van der Born, D.; Sewing, C.; Herscheid, J. D. M.; Windhorst, A. D.; Orru, R. V. A.; Vugts, D. J. *Angew. Chem. Int. Ed.* **2014**, 53, 11046. (x) Okusu, S.; Hirano, K.; Tokunaga, E.; Shibata, N. *ChemistryOpen* **2015**, 4, 581. (y) He, L.; Tsui, G. C. *Org. Lett.* **2016**, 18, 2800. (z) Yang, X.; He, L.; Tsui, G. C. *Org. Lett.* **2017**, 19, 2446. (aa) He, L.; Yang, X.; Tsui, G. C. *J. Org. Chem.* **2017**, 82, 6192.
- (9) (a) Iida, T.; Hashimoto, R.; Aikawa, K.; Ito, S.; Mikami, K. *Angew. Chem. Int. Ed.* **2012**, 51, 9535. (b) Honda, K.; Harris, T. V.; Hatanaka, M.; Morokuma, K.; Mikami, K. *Chem. Eur. J.* **2016**, 22, 8796. (c) Aikawa, K.; Maruyama, K.; Honda, K.; Mikami, K. *Org. Lett.* **2015**, 17, 4882. (d) Mikami, K.; Tomita, Y.; Itoh, Y. *Angew. Chem. Int. Ed.* **2010**, 49, 3819. (e) Aikawa, K.; Maruyama, K.; Nitta, J.; Hashimoto, R.; Mikami, K. *Org. Lett.* **2016**, 18, 3354.
- (10) Difluoromethylations with fluoroform reported by other groups: (a) Rioski, M. V.; Hart, A. D.; Colby, D. A. *Org. Lett.* **2013**, 15, 208. (b) Thomason, C. S.; Dolbier, W. R. *J. Org. Chem.* **2013**, 78, 8904. (c) Thomason, C. S.; Wang, L.; Dolbier, W. R. *J. Fluorine Chem.* **2014**, 168, 34. (d) Okusu, S.; Tokunaga, E.; Shibata, N. *Org. Lett.* **2015**, 17, 3802.
- (11) Hashimoto, R.; Iida, T.; Aikawa, K.; Ito, S.; Mikami, K. *Chem. Eur. J.* **2014**, 20, 2750.
- (12) (a) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, 97, 757. (b) Prakash, G. K. S.; Mandal, M. *J. Fluorine Chem.* **2001**, 112, 123. (c) Liu, X.; Xu, C.; Wang, M.; Liu, Q. *Chem. Rev.* **2015**, 115, 683.
- (13) **Typical Procedure for Difluoromethylation with CF₃H**
To a solution of 9-phenyl-9H-fluorene **1a** (0.10 mmol, 24.2 mg) in THF (1.0 mL) was added *n*-butyllithium solution (1.6 M in hexane, 0.11 mmol, 69 μ L) at -78°C . After stirring for 5 minutes at the same temperature, fluoroform (0.20 mmol, 4.5 mL) was bubbled slowly into the mixture via a gas-tight syringe. After stirring for 1 h at -78°C , the reaction was quenched with water. The organic layer was extracted with diethyl ether, washed with brine, and dried over anhydrous MgSO₄. After filtration, the solvent was removed under reduced pressure. The NMR yield was determined by using benzotrifluoride (BTF) as an internal standard. The residue was purified by silica-gel column chromatography (hexane/ethyl acetate, 50:1 as eluent) to afford **2a** (44% NMR yield, 37% isolated yield) as a colorless liquid.
Compound 2a: ¹H NMR (300 MHz, CDCl₃): δ = 7.81 (d, *J* = 7.6 Hz, 2 H), 7.50–7.44 (m, 4 H), 7.35–7.26 (m, 7 H), 6.12 (t, *J*_{H-F} = 55.5 Hz, 1 H); ¹³C NMR (75 MHz, CDCl₃): δ = 145.2 (t, *J*_{C-F} = 3.2 Hz), 141.3 (s), 138.5 (s), 128.8 (s), 128.6 (s), 127.9 (s), 127.6 (s), 127.4 (s), 126.6 (s), 120.2 (s), 117.7 (t, *J*_{C-F} = 248.7 Hz), 62.5 (t, *J*_{C-F} = 19.6 Hz); ¹⁹F NMR (282 MHz, CDCl₃): δ = -119.3 (d, *J*_{H-F} = 55.2 Hz, 2 F); FTIR (neat): 3062, 3037, 2961, 2928, 1497, 1450, 1376, 1128, 1064, 734 cm⁻¹; HRMS (APCI-TOF): *m/z* [M+H]⁺ calcd for C₂₀H₁₅F₂: 293.1142; found: 293.1143.
- (14) **Typical Procedure for Siladifluoromethylation with CF₃TMS**
To a solution of 9-phenyl-9H-fluorene **1a** (0.10 mmol, 24.2 mg) in THF (1.0 mL) was added *n*-butyllithium solution (1.6 M in hexane, 0.11 mmol, 69 μ L) at -78°C . After stirring for 5 minutes at the same temperature, CF₃TMS (0.20 mmol, 30 μ L) was added. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. The reaction was quenched with water, the organic layer was extracted with diethyl ether, washed with brine, and dried over anhydrous MgSO₄. After filtration, the solvent was removed under reduced pressure. The NMR yield was determined by using benzotrifluoride (BTF) as an internal standard. The residue was purified by silica-gel column chromatography (hexane/ethyl acetate, 50:1 as eluent) to afford **4a** as a colorless liquid.
Compound 4a: ¹H NMR (300 MHz, CDCl₃): δ = 7.82 (d, *J* = 7.6 Hz, 2 H), 7.60 (d, *J* = 7.6 Hz, 2 H), 7.52–7.44 (m, 4 H), 7.34–7.20 (m, 5 H), -0.50 (s, 9 H); ¹³C NMR (75 MHz, CDCl₃): δ = 146.8 (t, *J*_{C-F} = 4.4 Hz), 141.5 (s), 140.1 (s), 131.5 (t, *J*_{C-F} = 272.0 Hz), 128.8 (t, *J*_{C-F} = 2.7 Hz), 128.7 (s), 128.3 (s), 128.1 (s), 127.9 (s), 126.7 (s), 120.0 (s), 65.2 (t, *J*_{C-F} = 19.5 Hz), -3.8 (t, *J*_{C-F} = 2.3 Hz); ¹⁹F NMR (282 MHz, CDCl₃): δ = -107.7 (s, 2 F); FTIR (neat):

3060, 2958, 2899, 1495, 1449, 1253, 1075, 985, 847, 745 cm^{-1} ; HRMS (APCI-TOF): m/z $[\text{M}+\text{H}+\text{CH}_3\text{CN}]^+$ calcd for $\text{C}_{25}\text{H}_{26}\text{F}_2\text{NSi}$: 406.1803; found: 406.1818.

- (15) (a) McCluskey, G. E.; Watkins, S. E.; Holmes, A. B.; Ober, C. K.; Lee, J.-K.; Wong, W. W. H. *Polym. Chem.* **2013**, *4*, 5291. (b) Honmou, Y.; Hirata, S.; Komiyama, H.; Hiyoshi, J.; Kawauchi, S.; Iyoda, T.; Vacha, M. *Nat. Commun.* **2014**, *5*, 4666; and references cited therein.
- (16) (a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (b) Schlosser, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 376. (c) Hashimoto, R.; Iida, T.; Aikawa, K.; Ito, S.; Mikami, K. *Chem. Eur. J.* **2014**, *20*, 2750. (d) Nitta, J. *Bachelor Thesis*; Tokyo Institute of Technology, **2015**.
- (17) (a) Matthews, W. S.; Bares, J. E.; Bartmess, J. E.; Bordwell, F. G.; Cornforth, F. J.; Drucker, G. E.; Margolin, Z.; McCallum, R. J.; Vanier, N. R. *J. Am. Chem. Soc.* **1975**, *97*, 7006. (b) Symons, E. A. Clermont M. J. *J. Am. Chem. Soc.* **1981**, *103*, 3127.