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## COMMUNICATION

# Base-Mediated Defluorosilylation of *sp*<sup>2</sup> & *sp*<sup>3</sup> C–F Bonds

#### Xiang-Wei Liu, Cayetana Zarate and Ruben Martin\*

**Abstract:** The ability to selectively forge C-heteroatom bonds via C-F scission is typically accomplished by metal catalysts, specialized ligands and/or harsh conditions. Herein, we describe a base-mediated defluorosilylation of unactivated  $sp^2$  and  $sp^3$  C-F bonds that obviates the need for metal catalysts. This protocol is characterized by its simplicity, mild conditions and wide scope, even within the context of late-stage functionalization, constituting a complementary approach to existing C-Si bond-forming protocols.

The high binding affinity, improved bioavailability and enhanced metabolic stability of fluorinated compounds make them particularly attractive, yet prevalent, motifs in industrial endeavors, particularly in pharmaceuticals or molecules that display important biological activities.<sup>[1]</sup> In recent years, chemists have been challenged to turn the unusual high bond strength of sp<sup>2</sup> and sp<sup>3</sup> C-F bonds (~111-126 kcal/mol) - the strongest Cheteroatom bond linkages in nature - into a strategic advantage,[2] suggesting that late-stage C-F functionalization might serve as a new technology for rapidly generating structural diversity in drug discovery.<sup>[3]</sup> Despite the advances realized, C-F bond-functionalization remains primarily confined to C-C bondformations requiring transition metal catalysts, stoichiometric organometallics (Scheme 1, path a),[4] arynes[5] or nucleophilic aromatic substitutions (S<sub>N</sub>Ar) with activated fluoroarenes.<sup>[6]</sup> However, C-heteroatom bond-forming reactions via cleavage of unactivated C-F bonds still remain an elusive endeavour (path b),[7-8] representing a unique opportunity to improve our evergrowing synthetic arsenal via C-F bond-functionalization.<sup>[9]</sup>



Scheme 1. C-Heteroatom bond-formation via sp<sup>2</sup> & sp<sup>3</sup> C-F bond-cleavage.

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Organic silanes are valuable synthetic intermediates of utmost relevance in medicinal and material science.<sup>[10]</sup> Unlike classical methods for their synthesis that heavily rely on stoichiometric, yet highly reactive, organometallic species,<sup>[11]</sup> recent advances have led to the discovery of efficient transition metal-catalyzed silvlations of ubiquitous C-H<sup>[12]</sup> or C-(pseudo)halide bonds.<sup>[13]</sup> However, site-selectivity issues with unbiased substrates account for the former whereas the activation of particularly strong C-F bonds remains beyond reach in the later. Despite the advances realized, these techniques invariably require transition metal catalysts, specialized ligands and, in some cases, harsh reaction conditions. Therefore, at the outset of our investigations it was unclear whether it would be possible to design a direct silvlation of unactivated sp<sup>2</sup> & sp<sup>3</sup> C-F bonds that operated under mild conditions and in the absence of transition metals.<sup>[14]</sup> If successful, we recognized that such a scenario might unravel an opportunity to offer new vistas and complementary reactivity for the functionalization of unactivated C-F bonds.<sup>[9]</sup> In our continuing interest in designing new silvlation reactions,<sup>[15]</sup> we describe herein a base-promoted defluorosilylation of unactivated sp<sup>2</sup> and sp<sup>3</sup> C-F bonds. The protocol is distinguished by its mild conditions and ease of execution, thus representing a convenient platform to rapidly access valuable organic silanes, even at late-stages, and without recourse to transition metal catalysts, specialized ligands or organometallic reagents. We believe these results will foster systematic investigations for utilizing advanced fluorinated materials as new scaffolds for building up molecular complexity via C-F bond-cleavage.

	F	LiHMDS (2 equiv)	SiEt <sub>3</sub>
Ph	+ Et <sub>3</sub> SIBPIN	DME, rt	Ph
1a			2a
Entry	Deviation from standard conditions		<b>2a</b> (%) <sup>[a]</sup>
1	none		<b>91</b> <sup>[b]</sup>
2	NaHMDS instead of LiHMDS		52
3	KHMDS instead of LiHMDS		6
4	KOMe (KOtBu) instead of LiHMDS		0 (0)
5	LiOMe instead of LiHMDS		0
6	Cs <sub>2</sub> CO <sub>3</sub> instead of LiHMDS		0
7	LDA instead of LiHMDS		0
8	THF instead of DME		0
9	1,4-Dioxane instead of DME		0
10	DMSO instead of DME		0
11	HMPA instead of DME		0
12	Et <sub>3</sub> SiH instead of Et <sub>3</sub> SiBPin		0

Scheme 2. Optimization of the reaction conditions. 1a (0.20 mmol), Et<sub>3</sub>SiBPin (0.40 mmol), LiHMDS (0.40 mmol) in DME (0.40 mL) at rt for 16 h. <sup>[a]</sup> Yields determined by GC using decane as internal standard. <sup>[b]</sup> Isolated yield, average of two independent runs. DME = 1,2-dimethoxyethane; HMDS = hexamethyldisilazide; LDA = lithium diisopropylamide; DMSO = dimethyl sulfoxide; HMPA = hexamethylphosphoramide; Bpin = 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl.

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We began our study by evaluating the defluorosilylation reaction of 1a with readily accessible Et<sub>3</sub>SiBPin (Table 1).<sup>[16,17]</sup> The choice of Et<sub>3</sub>SiBPin was not arbitrary; unlike conventional arylsilylated reagents, Et<sub>3</sub>SiBPin offers the opportunity to functionalize selectively the resulting aryl-Si bond.<sup>[18]</sup> After some optimization,<sup>[19]</sup> a transition metal-free protocol based on LiHMDS in DME at rt provided the best results, affording ipsosilylated 2a in 91% isolated yield. These results are particularly noteworthy, as C-heteroatom bond formation via C-F cleavage typically falls under the realm of transition metal catalysis<sup>[7-9]</sup> or S<sub>N</sub>Ar reactions with activated fluoroarenes.<sup>[6]</sup> Under the limits of detection, not even traces of ortho- or meta-silylation were observed in the crude mixtures, thus arguing against a scenario based on aryne intermediates.<sup>[5]</sup> As shown in entries 2-4, countercations other than Li<sup>+</sup> resulted in a significant erosion in vield, thus suggesting that coordination of the fluorine atom to Li<sup>+</sup> was critical for success. This notion gains credence by observing a C-Si to C-B bond-forming selectivity switch depending on the nature of the aryl halide, with aryl iodides being particularly suited for a borylation event.<sup>[19,20]</sup> The nature of the silvlated reagent, counteranion and solvent was equally important (entries 5-12). As shown in entries 10-11, not even traces of 2a were observed with polar solvents typically employed in S<sub>N</sub>Ar reactions.<sup>[6]</sup> Additionally, the replacement of LiHMDS by common (in)organic bases or DME by other ethereal solvents failed to provide 2a (entries 5-9), thus showing the subtleties of our protocol.[21]



Scheme 3. Base-promoted defluorositylation of aryl fluorides. Conditions: see Scheme 2 (entry 1); yields of isolated products, average of two independent runs. <sup>[a]</sup> LiHMDS (1.50 equiv), PhMe<sub>2</sub>BPin (1.50 equiv). <sup>[b]</sup> LiHMDS (5 equiv), Et<sub>3</sub>SiBPin (5 equiv). <sup>[c]</sup> KO*t*Bu (3 equiv), Et<sub>3</sub>SiBPin (1.50 equiv).

Encouraged by these initial results, we sought to examine the generality of our base-mediated defluorosilylation event. As evident from the results compiled in Scheme 3, the substitution pattern on the arene was largely inconsequential, leading to the corresponding *ipso*-silylation in good to high yields with a wide

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variety of para-, meta- and ortho-substituted fluoroarenes.[21] Note, however, that moderate yields were generally observed for ortho-substituted analogues (2c, 2j). As shown for 2a', Me<sub>2</sub>PhSiBPin could also be used as silvl nucleophile with similar ease. Importantly, the reaction en route to 2a could easily be scaled up without significant erosion in yield.<sup>[19]</sup> Notably, the reaction operated equally well with non-conjugated fluoroarenes (2i-2l); in case of 2i, however, low yields were found with LiHMDS (<10%) when compared to KOtBu. Exhaustive silylation was observed for difluoroarenes (2f) whereas amines (2d, 2g) or acetals (2h) could perfectly be tolerated. Even methoxy residues (2e, 2j, 2l) or nitrogen-containing heterocycles did not interfere with productive C-Si bond-formation (2k, 2m and 2n). These results are particularly noteworthy, as it offers orthogonal reactivity to recent silvlation of C-OMe bonds<sup>[15b]</sup> or C-Si bondformations with electron-rich heterocycles.<sup>[22]</sup>



**Scheme 4.** Base-mediated defluorosilylation of *sp*<sup>3</sup> C–F bonds. Reaction conditions: see Scheme 2 (entry 1); yields of isolated products, average of at least two independent runs. <sup>[a]</sup> LiHMDS (1.50 equiv), PhMe<sub>2</sub>BPin (1.50 equiv).

A close inspection into the literature indicated that there is a paucity of ipso-functionalizations of unactivated sp3 C-F bonds,<sup>[23]</sup> particularly in the absence of transition metal catalysts or harsh conditions.<sup>[24,25]</sup> If successful, we recognized that extending the generality of our ipso-silylation to fluoroalkanes via sp<sup>3</sup> C-F cleavage might offer an opportunity to upgrade refrigerants, anesthesics or pharmaceuticals.<sup>[10]</sup> Gratifyingly, our LiHMDS-mediated protocol could be applied to sp<sup>3</sup> C-F scission under otherwise identical reaction conditions to those shown in Scheme 3, invariably affording 4a-4h in good to excellent yields (Scheme 4). As for Scheme 3, nitrogen-containing heterocycles (4e-4g)<sup>[22]</sup> or methoxy groups (4a, 4d)<sup>[15b]</sup> could perfectly be accommodated.[26,27] Of particular relevance is the successful preparation of 4c featuring two C-F bonds posessing different hybridized carbons.<sup>[28]</sup> Intriguingly, the silylation event occurred exclusively at the sp<sup>3</sup> C-F bond, leaving ample room for subsequent cross-couplings via sp<sup>2</sup> C-F bond-cleavage.<sup>[7-9]</sup>

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late-stage silvation of advanced fluorinated compounds



Scheme 5. Late-stage silylation via C-F scission & application profile.

With a reliable base-promoted defluorinative silulation of  $sp^2$  & sp<sup>3</sup> C–F bonds in hand, we next wondered whether our protocol could be applied within the context of late-stage silvlation of advanced fluorinated compounds. As shown in Scheme 5 (top), this turned out to be the case. Specifically, we could efficiently enable a C-Si bond-forming reaction with Blonanserin, an antipsychotic drug approved for the treatment of schizophrenia (7). Likewise, fluorinated estrone or  $\delta$ -tocopherol derivatives posed no problems, affording the defluorosilylation products 5 and 6 via either sp<sup>2</sup> or sp<sup>3</sup> C-F cleavage. The results shown in Scheme 5 (bottom) further illustrates, in preparative terms, the potential of our base-promoted defluorosilylation event as well as the utility of triethyl arylsilanes as functional handles via sp<sup>2</sup> C-Si cleavage.<sup>[17,18]</sup> While 8 was easily within reach via Pdcatalyzed C-H functionalization,<sup>[29]</sup> a formal ipso-halogenation of fluoroarenes could easily be effected en route to 9 and 10.



Scheme 6. Mechanistic rationale.

Although unraveling the mechanistic intricacies of this reaction should await further investigations, our available data can be interpreted on the basis of a silylborate of the formal composition [Et<sub>3</sub>SiBPin(N(SiMe<sub>3</sub>)<sub>2</sub>)]Li formed upon exposure of Et<sub>3</sub>SiBPin to LiHMDS (Scheme 6).<sup>[30]</sup> Such species might subsequently act as silyl anion surrogates in a concerted nucleophilic substitution at the *ipso* C–F site.<sup>[31,32]</sup> This notion gained credence by studying the stereochemical course of **11** and **12**; as shown, the defluorosilylation proceeded with neat inversion of configuration at C1, suggesting that cationic or radical-type pathways might not be operative. The superior reactivity of DME when compared to other ethereal solvents (Table 1) suggests a non-negligible role of denticity, solvation and/or aggregation on reactivity, likely via the involvement of a solvent-separated ion pair L.<sup>[33]</sup> At present, the significant lower reactivity of Na<sup>+</sup> or K<sup>+</sup> disilazide congeners (Scheme 2) is tentatively ascribed to the formation of a covalent Li–F bond, causing a significant elongation of the C– F linkage while facilitating a C–Si bond-formation via **II** or **III**.<sup>[34]</sup>

In summary, we have developed a base-promoted defluorosilylation of unactivated fluoroarenes and fluoroalkanes via  $sp^2$  or  $sp^3$  C–F bond-cleavage that obviates the need for transition metals or specialized ligands. The salient features of this method are the mild conditions (room temperature), ease of execution and wide scope, including late-stage defluorosilylation techniques. We anticipate that these findings will foster new investigations via the cleavage of other related unreactive bonds. Further work along these lines is currently underway.

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A base-promoted defluorosilylation of unactivated sp<sup>2</sup> and even sp<sup>3</sup> C–F bonds that obviates the need for transition metal catalysis, specialized ligands or harsh conditions has been developed. The salient features of this method are the mild conditions, ease of execution and wide substrate scope, even within the context of late-stage functionalization of advanced fluorinated building blocks, thus offering a complementary reactivity mode to existing silylation technologies.

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Title

Base-mediated defluorosilylation of

sp<sup>2</sup> & sp<sup>3</sup> C-F bonds