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Siladifluoromethylation and Deoxo-trifluoromethylation of P^V−H Compounds with $TMSCF_3$: Route to P^V−CF_2^- Transfer Reagents and P−CF_3 Compounds

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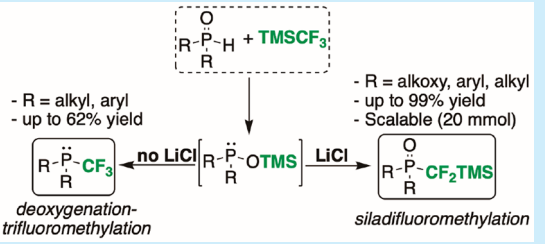
Supporting Information

ABSTRACT: A method for siladifluoromethylation of dialkyl phosphonates and secondary phosphine oxides with $TMSCF_3$ to produce nucleophilic P^V−CF_2− transfer reagents is disclosed, with multigram scale reactions included. Condition-dependent divergent reactivity under the established conditions is demonstrated by the formation of trifluoromethylphosphines. Both one-pot transformations are operationally simple and employ inexpensive materials. Mechanistic investigations suggest the divergent reactivity originates from a common intermediate, with Li^+ concentration directing the chemoselectivity.



Fine-tuning the chemical and physical properties of molecules through fluorofunctionalization is commonplace in materials[1] and medicinal[2] chemistry. The versatile −CF_2− unit, which is a bioisostere of etherial oxygens, carbonyls, secondary amides and methylenes, that also demonstrates lipophilic hydrogen bond donor properties,[3] has inspired a plethora of *gem*-difluorination[4] and difluoromethylation[5] protocols. A prime example of −CF_2− bioisosterism is the use of −CF_2P^V groups in creating metabolically stable, bioactive molecules,[6] especially nucleoside mono/di/triphosphate analogues.[7] The −CF_3 group has also shown remarkable applicability in the creation of new materials and bioactive compounds, spurring on a race for better trifluoromethylation protocols.[8]

$P^V CF_2TMS$ reagents, by virtue of their mild activation conditions, have been extensively used in reactions with electrophiles[9] and in cross-coupling[10] (Figure 1), with numerous scaffolds, having been functionalized. Variability of P^V substituents can potentially influence chemical/physical properties, but examples of such compounds are scarce. Known reagent preparations have not included such variability, with scope limited to −OEt and −O*i*-Pr derivatives. Despite the associated hazards, limited availability, and requirement of an additional silylation step,[11] they are accessed from the controlled substance CF_2Br_2[12] (Halon 1202): a class I ozone depleting substance and the most hazardous fluorobromocarbon known. Another approach involves C(sp^3)−H chlorination of diisopropyl ((methylthio)methyl)phosphonate, chlorine-fluorine exchange (with 3HF-Et_3N), activation with *n*-BuLi, and silylation[13] (Figure 2). P^V−CF_2H compounds have been prepared using $TMSCF_2Br$.[14] This work aims to provide access to such $P^V CF_2TMS$ and $P^V CF_2H$ compounds using inexpensive, safe reagents.

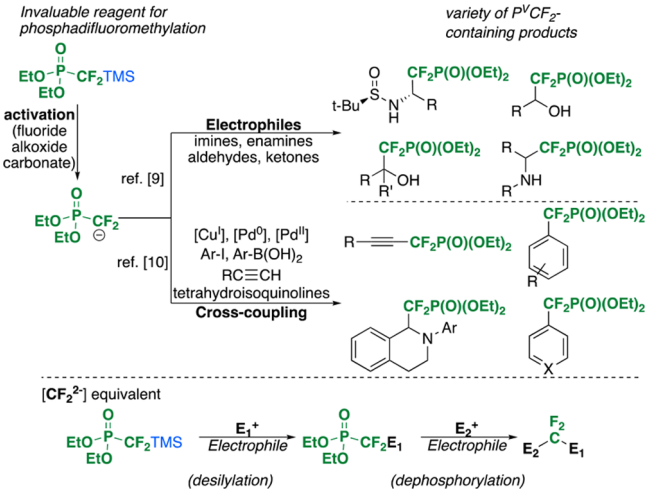


Figure 1. Extensive use of $P^V CF_2TMS$ reagents, mostly limited to diethyl phosphonate derivatives.

P^V−CF_3 compounds have been synthesized using CF_3Br in an Arbuzov-type reaction.[15] P−H trifluoromethylation has been shown using $TMSCF_3$ with (a) dialkyl phosphonates and copper(I),[16] (b) P^{III}−X compounds (X = F, NEt_2, OPh) and CsF.[17] Electrophilic-type trifluoromethylation with a Yagupolskii−Umemoto-type/Togni's reagent is also reported.[18] There are no reports of single-step deoxygenation−trifluoromethylation of P^V−H compounds to afford P^{III}−CF_3 compounds.

$TMSCF_3$ is a source of nucleophilic −CF_3,[19] −CF_2H,[20] and −C_2F_5,[21] and electrophilic singlet CF_2 carbene.[22] It can be

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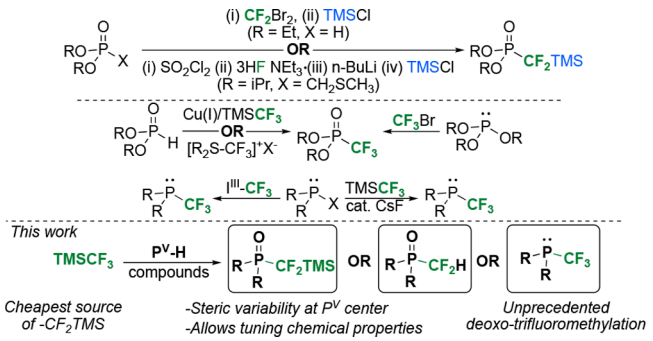
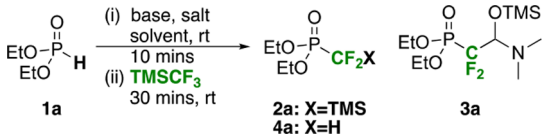


Figure 2. Reported syntheses of siladifluoromethyl and trifluoromethyl phosphorus compounds.

prepared from fluoroform[23] and is safer and less expensive than many other fluoroalkylation reagents. Using $TMSCF_3$ to add $-CF_2TMS$ to nucleophiles has garnered appreciable interest, allowing direct synthesis of less-accessible difluoromethylsilanes from a single $-CF_2-$ and TMS− source. The seminal work of Mikami and co-workers on the siladifluoromethylation of boron[24] and sp^3, sp^2, and sp carbon[25] centered nucleophiles is a prime example. An HMPA-mediated siladifluoromethylation of di/triarylmethanes is reported.[26] Our group recently detailed a synthesis of $S^{II}-CF_2H$ compounds via $S^{II}-CF_2TMS$ intermediates.[27]

Optimization trials (Table 1) were performed using **1a**. Among the bases screened, hydrides proved most effective,

Table 1. Select Optimization Studies on Diethyl Phosphonate (1a)[a]

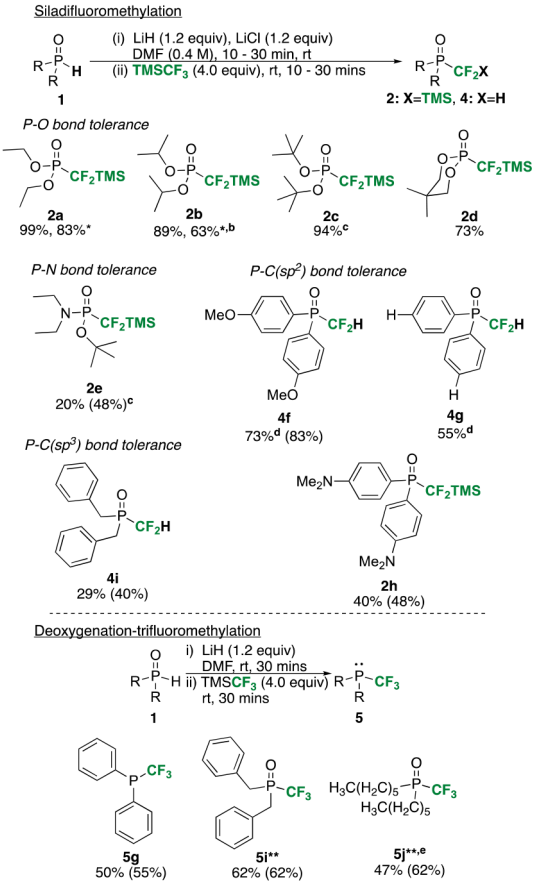


				NMR Yield[b] (%)		
trial[a]	salt[e]	base[e]	$TMSCF_3$ (equiv)	2a	3a	4a
1	LiI	LiOtBu	2.5	22	0	11
2	LiI	LiH	2.5	66	0	0
3	LiI	NaH	2.5	66	0	0
4[c]	LiI	–	2.5	0	0	0
5	NaCl	NaH	2.5	0	89	3
6	NaI	NaH	2.5	5	24	5
7	LiCl	NaH	2.5	73	4	2
8	LiCl	LiH	2.5	84	0	0
9[d]	LiCl	LiH	4.0	99	0	0

[a]Unless specified, trials were performed using **1a** (0.5 mmol), in DMF (0.2 M). [b]Based on ^{19}F NMR using fluorobenzene (0.5 mmol) as an internal standard. [c]$LiBF_4$ (1.2 equiv) was added. [d]Reaction was performed in DMF (0.4 M). [e]1.2 equiv.

affording **2a** in 66% yield (trials 2 and 3). Amide and alkoxide bases proved ineffective for this substrate, with appreciable decomposition of **1a**. Under these conditions, no reaction was observed in THF, Et_2O, hexanes, MeCN, or DMPU; with the latter undergoing significant decomposition. Binary systems of DMF with THF, hexanes, MeCN, or Et_2O did not produce favorable results. Our working hypothesis was that the reaction proceeded through a difluorocarbene intermediate; therefore, utilizing lithium or sodium salts could accelerate decomposition of $[CF_3]^-$ to difluorocarbene. Interestingly, upon substituting LiI with NaCl, **2a** was not observed; the hitherto unknown **3a** was formed selectively (trial 5), highlighting the need for Li^+.[28] The combination of LiH and LiCl afforded **2a** in near-quantitative yields (trial 9). The method was extended to a series of phosphonates and phosphine oxides (see Scheme 1).

Scheme 1. Siladifluoromethylation and Deoxotrifluoromethylation of P−H Compounds[a]



[a]Reactions performed with 0.5 mmol of **1**. Yields in parentheses determined by ^{19}F NMR of reaction mix with PhF (0.5 mmol) as internal standard. Single asterisk symbol (*) indicates that 20 mmol of **1** was used; double asterisk symbol (**) indicates that the component has been oxidized for easy isolation. [b]2.5 equiv $TMSCF_3$. [c]2.0 equiv LiOtBu, 2.0 equiv LiCl. [d]4.0 equiv LiCl. [e]1.2 equiv LiCl added.

Phosphonate **2a**, used extensively in phosphadifluoromethylation reactions,[9,10] was obtained in near-quantitative yield (99%) (Scheme 1). To investigate steric effects at the P atom, **2b** was prepared from **1b** in excellent yield (89%). Even the egregiously sterically encumbered **1c** underwent facile transformation to **2c** (94%). At 20 mmol scale, **2a** (83%, 4.3 g) and **2b** (63%, 3.6 g) were obtained in high yields, demonstrating scalability and applicability in bulk reagent synthesis. Although reagents **2a**−**2c** enable steric variability at the P center, the cleavable alkoxy groups may limit applicability in some scenarios. Cyclic phosphonate **2d** was prepared in excellent yield (73%) as a potentially more-stable reagent. Diphenyl phosphonate and dibenzyl phosphonate, however, did not produce the corresponding products **2**, possibly because of the

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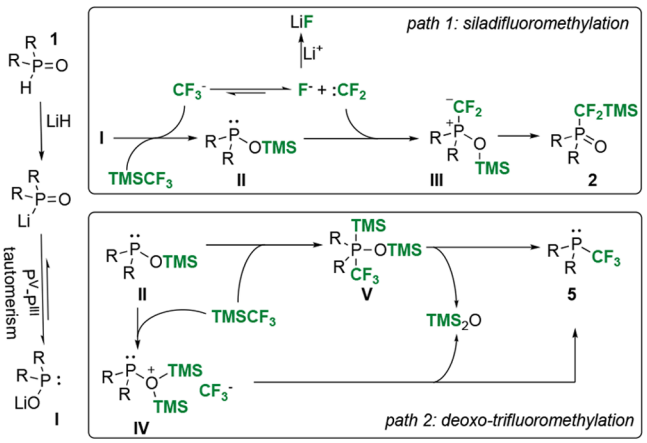
enhanced leaving group ability of the −OR groups. Nonetheless, the method seems well-suited for dialkyl phosphonates. To investigate the tolerance of P−N bonds, **1e** was subjected to the reaction conditions, and phosphonamidate **2e** (20%) was isolated. Diarylphosphine oxides **4f** and **4g** were prepared in good to excellent yields (55% and 73%) as a mixture of the corresponding P^V−CF_2TMS and P^V−CF_2H compounds; thus, they were isolated as the corresponding P^V−CF_2H products. Interestingly, the most electron-rich phosphine oxide **2h** was obtained selectively as the P^V−CF_2TMS compound (40%). The greater electron density at the P atom, leading to a less-stable anion upon desilylation, may be responsible for this heightened stability. A similar reaction with bis(4-(trifluoromethyl)phenyl)phosphine oxide did not produce any significant amount of product **2**. It appears that electron-deficient aryl units are not compatible with this procedure. Difluoromethyl dialkyl phosphine oxide **4i** was obtained in 29% yield.

Surprisingly, in the absence of LiCl, **1i** showed an unprecedented deoxo-trifluoromethylation to afford the corresponding trifluoromethyl phosphine **5i** in 62% yield (Scheme 1), which underwent slow oxidation in air. Similarly, **5j** was obtained in good yield (47%, 62% by NMR). These results demonstrate a divergence in reactivity under similar conditions, dictated by the amount of LiCl present. Finally, **5g** was obtained (50%) as an air-stable solid. This is the first report of a tandem deoxygenation−trifluoromethylation of secondary phosphine oxides using $TMSCF_3$ to produce $-CF_3$ phosphines, wherein the oxidation state of P changes from +5 to +3.

To elucidate potential reaction pathways (Scheme 2) and probe intermediates involved in the divergent reactivity,

Scheme 2. Plausible Reaction Pathways

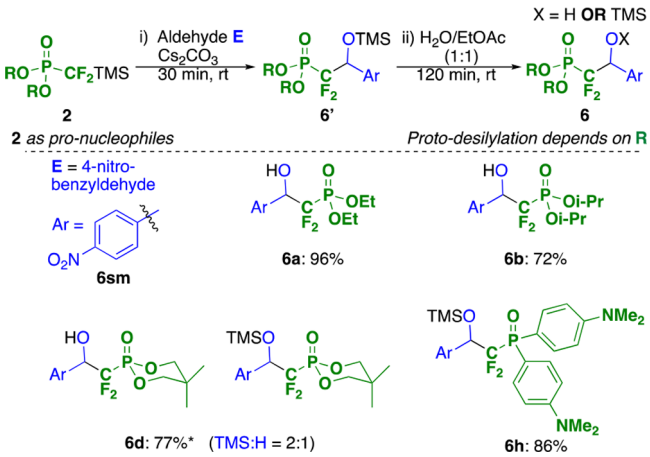


control experiments were performed (see the Supporting Information for full discussion of experiments). We envision that the divergent reactivity results from differences in the mode of reaction of intermediate **II** with $TMSCF_3$. In *path 1*, we propose that intermediate **II** is formed by silylation of **I** with $TMSCF_3$. This releases CF_3^- that will decompose in the presence of excess Li+ to produce electrophilic difluorocarbene. Trapping of difluorocarbene by **II** may result in the ylide-intermediate **III**, which could undergo an intramolecular or intermolecular silylation at the CF_2 carbon to afford product **2**.

In contrast, *path 2* may be a consequence of an additional silylation of **II** by another equivalent of $TMSCF_3$, producing either the oxonium trifluoromethide **IV** or trifluoromethyl-phosphorane **V**. Similar to the mechanism of deoxygenation (reduction) of phosphine oxides using hexachlorodisilane, a reductive elimination of TMS_2O would produce compound **5**.

As a demonstration of their synthetic utility, **2a**, **2b**, **2d**, and **2h** were reacted with **6sm** to produce P^VCF_2− compounds **6** (see Scheme 3). Interestingly, the stability of the O−TMS

Scheme 3. Demonstration of 2 as Reagents and the Significance of Variability at P[a]



[a]Unoptimized, isolated yields. See the Supporting Information for full experimental details. The single asterisk symbol (*) indicates that TMS may be fully cleaved on prolonged stirring.

bond depends on the identity of the R groups at P. **6a** and **6b** were readily formed. **6′d** underwent slower hydrolysis under the same conditions, producing a mixture of O−H and O−TMS compounds. **6h** was unreactive to the hydrolytic conditions. The difference in stability to the basic, aqueous conditions reinforces the importance of variability at the P atom in tuning the chemical properties of molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00381.

Procedures, characterization, and images of spectra (PDF)

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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