Fluorination Hot Paper

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Photoredox Activation of SF_6 for Fluorination

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Abstract: *We report the first practical use of SF_6 as a fluorinating reagent in organic synthesis. Photoredox catalysis enables the in situ conversion of SF_6, an inert gas, into an active fluorinating species by using visible light. Under these conditions, deoxyfluorination of allylic alcohols is effected with high chemoselectivity and is tolerant of a wide range of functional groups. Application of the methodology in a continuous-flow setup achieves comparable yields to those obtained with a batch setup, while providing drastically increased material throughput of valuable allylic fluoride products.*

The incorporation of fluorine into a molecule can dramatically alter its properties and impart unique or desirable characteristics.[1] Despite their utility, currently available fluorinating reagents for preparing organofluorines have significant limitations and fluorination remains an important challenge. In particular, the widely utilized sulfur-based nucleophilic reagents, such as DAST (**1**; Figure 1 A), can be explosive, lack functional-group tolerance, generate significant side products, and be prohibitively expensive.[2,3] The recently disclosed 2-pyridinesulfonyl fluoride (PyFluor, **2**) is currently the exception within this class in that it is accessible from inexpensive reagents, and exhibits both high stability and chemoselectivity.[3] Owing to the scarcity of suitable nucleophilic fluorinating reagents we sought to develop a new chemoselective, safe, and inexpensive alternative that could offer complementary reactivity to available methods. Herein we report the first practical use of sulfur hexafluoride (SF_6) as a fluorinating reagent in organic synthesis.

Sulfur hexafluoride is an inexpensive, inert gas, and thus would be an attractive source of fluorine atoms. Although it is widely available owing to its industrial applications, examples of its use in organic synthesis remain scarce.[4,5] Furthermore, the only successful examples of C–F bond formation with SF_6 involve gas-phase reaction conditions or extremely high temperatures and pressures,[6] highlighting the difficulty of using this otherwise inert gas as a fluorination reagent (Figure 1 B)

A mechanistically distinct approach to accessing highly reactive species is photoredox catalysis (Figure 2).[7] Based on previous reports describing the use of SF_6 as an electron scavenger[8] we hypothesized that SF_6 may engage in single-electron-transfer processes. In the proposed pathway

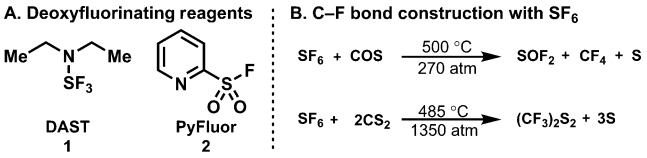

Figure 1. A) Commonly employed sulfur-based deoxyfluorination reagents. B) Examples of C–F bond formation with SF_6.

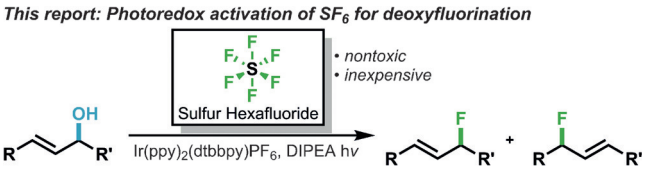

Figure 2. Deoxyfluorination of allylic alcohols by photoredox catalysis using SF_6.

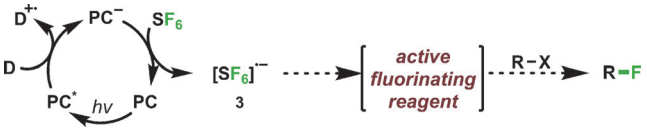

Figure 3. Photoredox activation of SF_6.

(Figure 3), a photocatalyst in its excited state would first transfer an electron to SF_6, generating an SF_6 radical anion (**3**). Subsequent fragmentation of **3** would lead to the in situ formation of several anionic and radical fluorine species[9] which could perform fluorination.

Given the reactivity of the established sulfur-based nucleophilic fluorinating reagents,[2] we envisioned that **3** or its fragmentation products may effect deoxyfluorination. We therefore began our investigations by exposing various alcohols to commonly employed photoredox conditions using $Ru(bpy)_3(PF_6)_2$ as a catalyst, diisopropylethyl amine (DIPEA) as a stoichiometric reductant, and blue LED (470 nm) irradiation. Allylic alcohol **4** successfully underwent deoxyfluorination to yield the corresponding allylic fluorides **5l** and **5b** in a combined 27% yield and a 1.7:1 ratio of linear (l) to branched (b) isomers (Table 1, entry 1). As a result of the particularly high value of allylic fluorides as versatile synthons and bioactive compounds,[10] we targeted deoxyfluorination of allylic alcohols by SF_6 for further development.

Systematic optimization studies[11] revealed that DIPEA was critical for promoting the desired reactivity. Replacement of DIPEA with less-hindered reductants led to decreased yields and increased formation of ammonium adducts[12] (entry 2). In MeCN, additional acetamide byproducts, presumably formed through Ritter-type reaction with the

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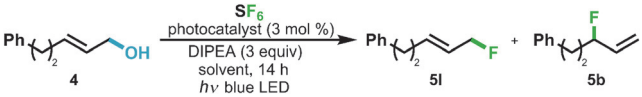
Table 1: Optimization of deoxyfluorination using SF_6.



Entry	Catalyst	Solvent	Conv.[a]	Yield (l:b)[a]
1[b,c]	$Ru(bpy)_3(PF_6)_2$	MeCN	74	27 (1.7:1)
2[b,d]	$Ru(bpy)_3(PF_6)_2$	MeCN	94	8 (3:1)
3[b,c]	$Ru(bpy)_3(PF_6)_2$	DMSO	8	4 (1:1)
4[b,c]	$Ru(bpy)_3(PF_6)_2$	*t*AmOH	34	14 (2.5:1)
5[b,c]	$Ru(bpy)_3(PF_6)_2$	DCE	90	32 (1.3:1)
6[e]	$Ru(bpy)_3(PF_6)_2$	DCE	93	32 (1.3:1)
7[e]	$Ir(ppy)_2(dtbbpy)PF_6$	DCE	96	55 (1.2:1)
8[e,f]	$Ir(ppy)_2(dtbbpy)PF_6$	DCE	75	38 (1.7:1)

[a] Determined by ^1H NMR with dimethyldiphenylsilane as an internal standard. [b] Reaction run for 24 h. [c] 10 equiv DIPEA. [d] 10 equiv N(*n*-Bu)$_3$. [e] 5 mol% catalyst. [f] $NEt_3{\cdot}3HF$ (1 equiv) added.

solvent, were also isolated. Based on this observation and the significant solvent effects exhibited in heterogeneous[13] and nucleophilic fluorination reactions,[1] several solvents were evaluated. While decreased conversions and yields were observed for highly polar (DMSO, entry 3) and protic solvents (*t*AmOH, entry 4), the use of the less polar dichloroethane (DCE) gave an improved 32% yield (1.3:1 l:b) of **5** (entry 5).

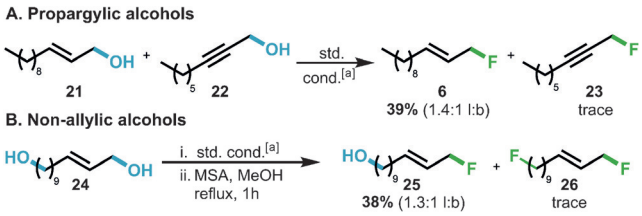
The reaction was also greatly accelerated in DCE providing identical yields in nearly half the time (14 vs. 24 h, entries 5–6). These results suggest that the reaction outcome relies on both the solvation of the active fluorinating reagent and the solubility of SF_6, which is higher in nonpolar solvents.[14] Further improvement in reactivity was provided by changing the photocatalyst to $Ir(ppy)_2(dtbbpy)PF_6$, which has a higher solubility in DCE, allowing for the amount of DIPEA to be reduced from 10 equivalents to 3 equivalents (entry 7). Under these conditions, a 55% yield of **5** (1.2:1 l:b) was achieved. To increase reaction yields, exogenous fluoride sources, such as triethylamine-HF and TBAT,[11] were also investigated, but no improvement in yield was observed (entry 8).

With the optimized reaction conditions in hand, we investigated the substrate scope of this transformation (Table 2). Deoxyfluorination of both primary (**6**) and secondary (**7**) allylic alcohols proceeded efficiently with SF_6. Additionally, the reaction could be performed on a variety of substitution patterns (**8**–**10**). More complex and sterically congested alcohols (**11**, **14**–**15**) also performed well. In general, most substrates exhibited a preference for direct substitution (α) over allylic substitution (γ) (e.g. **6** and **7** arise from the linear and branched allylic alcohols, respectively). This selectivity is enhanced with increased substitution at the γ-position (**9**, **12**) giving rise to linear:branched ratios as high as 11.3:1. Tertiary allylic alcohols, however, are unreactive (**13**).

This method is also tolerant of a wide range of functional groups including arenes (**5**), unprotected amines (**16**), heterocycles (**17**, **19**), amides (**18**), carbamates (**19**) and aldehydes (**21**). Notably, substrates possessing carbonyl groups (**18**–**20**) do not undergo competing *gem*-difluorination or form acyl fluorides as with alternative reagents.[15]

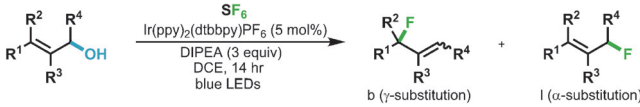
Remarkably, both propargylic (**22**; Scheme 1 A) and non-allylic alcohols (**24**; Scheme 1 B) could be used without significantly hindering the formation of **6** and **25**, respectively, or undergoing deoxyfluorination, which allows the reaction to be performed in the presence of unprotected non-allylic alcohols (Scheme 1). To our knowledge, this is the first example of the ability to differentiate between alcohols in this way, demonstrating the complementarity of deoxyfluorination with SF_6.

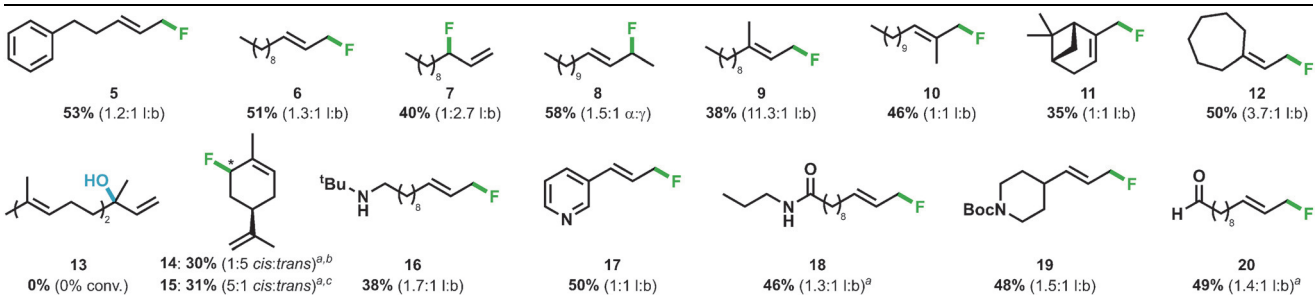
One area of chemistry that can provide considerable improvements to both photochemical and multiphasic reac-



Scheme 1. Selective deoxyfluorination. [a] SF_6, $Ir(ppy)_2(dtbbpy)PF_6$ (5 mol%), DIPEA (3 equiv), DCE (0.075 M), irradiation with blue LEDs, room temperature, 14 h. Linear:branched (l:b) ratio determined by NMR spectroscopic analysis.

Table 2: Scope of deoxyfluorination.





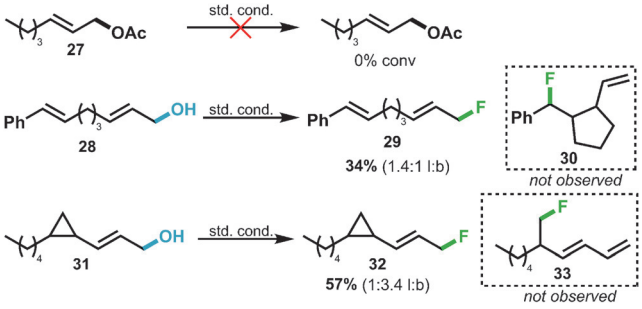
[a] Run at 60 °C. [b] From (−)-*trans*-carveol. [c] From (−)-*cis*-carveol. Linear:branched (l:b) ratio determined by NMR spectroscopic analysis.

tions is continuous flow.[16] Owing to decreased path lengths and increased interfacial area, mass- and energy-transfer rates are significantly enhanced in such systems, often providing superior results relative to batch reactions.[17] The ability to precisely control reaction conditions can also improve scalability and safety.

To examine these advantages with regard to the developed methodology, a simple flow setup was assembled (Scheme 2 A). Within it, substrate, catalyst, and reductant are pumped as a single stream and then combined with gaseous SF_6 via a Y-mixer (M1). The flow rate of SF_6 is adjusted to create a uniform 1:1 gas:liquid segmented ("slug") flow in the reaction line. Prior to irradiation, the two phases mix in R_1 (residence time: $t_R = 1$ min) before entering R_2 ($t_R =$ 15 min), which is illuminated by blue LEDs. Following the reaction, a back-pressure regulator (BPR) is used to place the entire system under 100 psi of pressure and increase the solubility of SF_6 in solution.

Under the optimized conditions, **6** was furnished in 79% yield relative to conversion of starting material, with a total residence time of 16 min, as compared to a 55% yield obtained in 14 h in batch (entries 1 and 3 in Scheme 2). Similar improvements were also observed for **11** and **12** (Scheme 2 B). Interestingly, in continuous flow, starting material is consumed within 2 min, generating the desired products as well as a previously unobserved intermediate, most consistent with $(RO)_2SF_4$. Over the course of the reaction, this intermediate is gradually converted back into starting material, preventing undesired side reactions. Given that elevated pressure (100 psi) did not produce similar conversions and yields in batch, it is likely that the increased pressure, mass-transfer, and interfacial area of the continuous-flow system all contribute to the formation of the intermediate and the improved yield-to-conversion ratio. Also noteworthy are the safety and throughput enabled under continuous flow. In the system, SF_6 can be easily handled with use of a BPR, allowing for the elevated pressures utilized to be achieved safely and controllably. Additionally, the assembled setup (2.7 mL in volume) was capable of almost five times the material throughout (0.19 mmol product/h vs. 0.04 mmol/h in batch).

We also carried out preliminary investigations of the mechanism of this transformation. In particular, we looked to gain better understanding of the nature of C–F bond formation. Prior to C–O bond cleavage, we anticipated that the alcohol would likely attack the sulfur atom of some SF_x species, since a similar step has been proposed for other sulfur-based deoxyfluorination reagents. As would be expected based on this proposal, when oxygen was protected (**27**), no reactivity was observed (Scheme 3). Furthermore, the formation of an O–S bond is supported by a dialkyl sulfite side product[13] observed in small quantities under the reaction conditions.

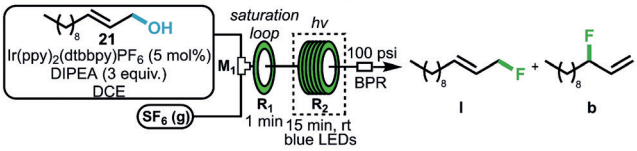


Scheme 3. Standard conditions (std. cond.): SF_6, $Ir(ppy)_2(dtbbpy)PF_6$ (5 mol%), DIPEA (3 equiv), DCE (0.075 M), irradiation with blue LEDs, room temperature, 14 h. Linear:branched (l:b) ratio determined by NMR spectroscopic analysis.

We further hypothesized that C–O bond cleavage could occur via a one- or two-electron process. The addition of one equivalent of TEMPO, however, had little effect on the reaction, giving a 47% yield (1.4:1 l:b) of **6** compared to 55% yield obtained in its absence. Additionally, no evidence for the formation of TEMPO adducts was observed in these reactions suggesting the absence of fluorine radicals and sufficiently long-lived radical intermediates of the starting material. The two-electron nature of C–F bond formation was further supported by radical clock experiments (Scheme 3). If during the course of the reaction an allylic radical is generated via C–O bond homolysis, a 5-*exo*-trig cyclization or radical cyclopropane ring opening would be expected to occur for substrates **28** and **31**, respectively. However, neither **30** nor **33** were observed (Scheme 3).

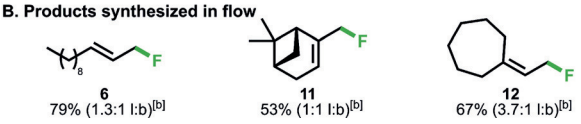
Although further studies are necessary to reveal mechanistic details, preliminary experiments indicate that the mechanism of this deoxyfluorination may share features with that of the chlorination of alcohols with thionyl chloride. In this case, C–O bond cleavage precedes C–X bond formation from an undissociated ion pair. As noted, the formation of both ammonium salts and Ritter-type products derived from the allylic alcohol were observed, suggesting the presence of an intermediate with significant cationic character. Furthermore, deoxyfluorination of *trans* and *cis*-(–)-carveol proceeded with overall retention of stereochemistry

A. Continuous-flow deoxyfluorination using SF_6



Entry	Method	Residence time (min)	Conv.[a]	Yield (l:b)[a]
1	batch	840	100	55% (1.2:1)
2	batch	16	41	16% (1:1)
3	flow	16	58	45% (1.1:1)

B. Products synthesized in flow



Scheme 2. Continuous-flow deoxyfluorination. [a] Determined by ^{1}H NMR with dimethyldiphenylsilane as an internal standard. [b] Yield relative to conversion of starting material.

(Table 2, **14** and **15** respectively), which is also observed in the reaction of allylic alcohols with thionyl chloride.[18]

Taken together these results support a mechanism in which the alcohol is first activated via O–S bond formation resulting in a R-O-SF_x intermediate. An intimate ion pair is then formed by C–O bond cleavage allowing for fluoride to be delivered from the generated $[OSF_x]^-$ anion, which serves as the active fluorinating reagent, producing the observed products with retention of stereochemistry. The additional stabilization provided by the adjacent alkene facilitates formation of the proposed ion pair, enabling allylic alcohols to be uniquely reactive under these conditions. Of particular note, this methodology offers a stereochemical outcome complementary to most currently available nucleophilic fluorinations. When deoxyfluorination of *trans* and *cis*-(−)-carveol is performed with DAST, *cis*/*trans* ratios of 1:1.5 and 1:5.7, respectively, were observed, as compared to ratios of 1:5 (**14**) and 5:1 (**15**) obtained using SF_6.

In summary, we have developed the first example of the use of SF_6 as a selective fluorinating reagent in organic synthesis via a novel activation method. As a reagent, SF_6 is unparalleled in its safety, and is only a fraction of the cost of comparable reagents (under \$4 mol^{-1}, Airgas). In application to the deoxyfluorination of allylic alcohols, SF_6 was shown to be highly chemoselective and tolerant of a wide array of functional groups, supplying good to moderate yields of the corresponding allylic fluorides, linear to branched ratios as high as 11.3:1, and reactivity patterns complementary to current methods. The continuous-flow format was also shown to be beneficial, providing improved yields, operational simplicity, and substantially higher product throughput. Lastly, the photoredox activation of SF_6 demonstrated in this study provides a basis to explore the broader applications of SF_6 as a reagent in organic synthesis.

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Keywords: alcohols · continuous flow · fluorination · photoredox catalysis · sulfur hexafluoride

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