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# **Open-Shell Fluorination of Alkyl Bromides: Unexpected Selectivity in a Silyl Radical-Mediated Chain Process**

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Supporting Information Placeholder

ABSTRACT: We disclose a novel radical strategy for the fluorination of alkyl bromides via the merger of silvl radicalmediated halogen-atom abstraction and benzophenone photosensitization. Selectivity for halogen-atom abstraction from alkyl bromides is observed in the presence of an electrophilic fluorinating reagent containing a weak N-F bond despite the predicted favorability for Si-F bond formation. To probe this surprising selectivity, preliminary mechanistic and computational studies were conducted, revealing that a radical chain mechanism is operative in which kinetic selectivity for Si-Br abstraction dominates due to a combination of polar effects and halogen atom polarizability in the transition state. This transition metal-free fluorination protocol tolerates a broad range of functional groups, including alcohols, ketones, and aldehydes, which demonstrates the complementary nature of this strategy to existing fluorination technologies. This system has been extended to the generation of gem-difluorinated motifs, which are commonly found in medicinal agents and agrochemicals.

The properties of alkyl fluorides, and their unique impact on organic molecules, have been exploited in the areas of pharmaceutical, agrochemical, and material sciences.<sup>1–3</sup> The increasing demand for novel mechanisms that allow C–F bond installation to be broadly applicable, operationally simple, and amenable to early or late stage implementation has greatly driven the community's interest in expanding the fluorination toolbox. Established protocols for the generation of C(sp<sup>3</sup>)–F bonds include deoxyfluorination of alcohols, hydrofluorination of alkenes, decarboxylative fluorination of acids, and radical C–H fluorination.<sup>4</sup> Given that these valuable technologies convert common organic functional groups to fluorine substituents, it is remarkable to consider that a general protocol for the transformation of a broad range of alkyl bromides into alkyl fluorides remains elusive.<sup>5–7</sup>

Silicon-centered radicals have long been known to serve as potent halogen-atom abstraction agents, forming alkyl radicals from the corresponding bromides at near-diffusion-limited reaction rates.<sup>8</sup> Recently, our laboratory has introduced the concept of photocatalytically-generated silyl radicals for the formation of alkyl and aryl radicals from their corresponding bromides using visible light. This open-shell halide activation mechanism has subsequently been incorporated into a variety of metallaphotoredox reaction designs including nickel- and copper-catalyzed cross-couplings of value to the medicinal chemistry sector.<sup>9</sup> With these technologies in mind, and given



Figure 1. Silyl radical-mediated fluorination of alkyl bromides

the widespread availability of alkyl bromides, we hypothesized that silyl radical activation in combination with radicophilic fluorine sources might allow ambient temperature access to  $C(sp^3)$ –F bonds in a generic fashion using a photocatalyst, visible light, and a mild fluorinating agent. Notably, an openshell fluorination strategy should provide complementary scope



BzN alkyl b	Br 1 e	1 mol% photoc quiv. Si• source, 3 e 1:1 MeCN/H <sub>2</sub> O (0. r.t., 40 W blue	catalyst iquiv. F <sup>+</sup> source .1 M), 2 equiv. base e LEDs, 8 hr	BzN F	
entry	photocatalyst	Si• source	F <sup>+</sup> source	base	yield
1 2 3 4 5 6 7 8	PC-1 PC-2 PC-2 PC-2 PC-2 PC-2 none benzophenone <sup>c</sup>	(TMS) <sub>3</sub> SiH (TMS) <sub>3</sub> SiH (TMS) <sub>3</sub> SiH (TMS) <sub>3</sub> SiOH <sup>b</sup> (TMS) <sub>3</sub> SiOH <sup>b</sup> (TMS) <sub>3</sub> SiOH <sup>b</sup> (TMS) <sub>3</sub> SiOH <sup>b</sup> (TMS) <sub>3</sub> SiOH <sup>b</sup>	Selectfluor NFSI NFSI NFSI NFSI NFSI NFSI	Na <sub>2</sub> HPO <sub>4</sub> Na <sub>2</sub> HPO <sub>4</sub> Na <sub>2</sub> HPO <sub>4</sub> Na <sub>2</sub> HPO <sub>4</sub> K <sub>3</sub> PO <sub>4</sub> K <sub>3</sub> PO <sub>4</sub> K <sub>3</sub> PO <sub>4</sub>	1% 31% 46% 76% 87% 49% 22% 86%
$F_{3}C$ $F_{6}F$ $F_{6}F$ $F_{6}F$ $F_{7}C$ $F$			$ \begin{array}{c} & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & $		

<sup>*a*</sup> 1.5 equiv. <sup>*b*</sup> 1.75 equiv. <sup>*c*</sup> 2.5 mol%

to classical substitution methods. While an open-shell fluorination strategy has been developed for tertiary alkyl bromides,<sup>7</sup> a silyl radical-mediated protocol should allow for a broad range of alkyl bromides to be converted to their corresponding alkyl fluorides.

From the outset, we recognized a significant challenge to achieving the desired selectivity for C-F bond formation using a silyl radical/bromine abstraction approach. Specifically, the required chemoselectivity of silyl radical abstraction from an alkyl bromide in the presence of an electrophilic fluorinating reagent (e.g., Selectfluor) appeared to be intrinsically problematic. First, there is large thermodynamic driving force for the formation of a strong Si-F bond via silyl radical abstraction from a weak N-F bond (63 kcal/mol for NFSI)<sup>10</sup> versus formation of the weaker Si-Br bond via desired abstraction from the alkyl bromide C-Br bond (~70 kcal/mol).<sup>1</sup> Second, polar effects in the transition state should favor abstraction from the electrophilic fluorinating reagent over the alkyl bromide, as the partial negative charge buildup in the transition state during abstraction by a nucleophilic siliconcentered radical<sup>12</sup> can be better stabilized by the electrondeficient nitrogen atom of an electrophilic fluorinating reagent than the carbon atom of the alkyl bromide (Figure 1). While these factors both favor the undesired abstraction, we were aware that the rates of silyl radical abstraction from C-X bonds are often dependent on the degree of atom polarizability of the halogen atom,<sup>13</sup> an aspect that should favor abstraction of the more polarizable bromine atom in lieu of a fluorine atom, thus leading to the desired selectivity.

Given the difficulties in predicting a priori which factors would impact the kinetic selectivity between these pathways, we chose to incorporate high throughput experimentation

Scheme 1. Proposed radical chain initiation and propagation



(HTE) in an effort to uncover which combination of fluorination sources, solvent polarity, and abstraction agents might deliver proof of concept, chemoselectivity, and, thereafter, broad scope. Because the mechanism for silvl radical generation<sup>9</sup> and fluorine atom transfer<sup>14,15</sup> should be similar to those previously proposed by our laboratory, we began our investigation by exposing 1-benzoyl-4-bromopiperidine to visible light irradiation (40 W blue LEDs) in the presence of [Ir(dF(CF<sub>3</sub>)ppy)<sub>2</sub>(dtbbpy)]PF<sub>6</sub> (**PC-1**), tris(trimethylsilyl)silane [(TMS)<sub>3</sub>SiH] as the silvl radical agent, Selectfluor as the fluorine source, along with Na<sub>2</sub>HPO<sub>4</sub> in MeCN/H<sub>2</sub>O. Despite the potential challenges of this approach, we observed 1% of the desired fluoroalkyl adduct (Table 1, entry 1), presumably due to photocatalytic reduction  $(E_{\frac{1}{2}}^{\text{red}}[Ir^{\text{III}}/Ir^{\text{II}}] = -1.37 \text{ V vs.}$ SCE in MeCN)<sup>9</sup> of the electrophilic fluorine source (Selectfluor,  $E_{pc} = +0.33$  V vs. SCE in MeCN)<sup>15</sup> being the dominant pathway.

Using a high-throughput evaluation protocol, we next evaluated a broad range of photocatalysts and electrophilic fluorine sources, and quickly determined that the desired 4-fluoro-piperidinyl adduct 1 could be obtained in 46% yield using *N*-fluorobenzenesulfonimide (NFSI) ( $E_{pc} = -0.78$  V vs. SCE)<sup>14</sup> in combination with the photocatalyst **PC-2**, [Ir(dF(CF<sub>3</sub>)ppy)<sub>2</sub>((5,5'-CF<sub>3</sub>)bpy)]PF<sub>6</sub> ( $E_{y_2}^{red}$ [Ir<sup>IV</sup>/Ir<sup>III</sup>] = -0.42 V vs. SCE in MeCN)<sup>16</sup> (entries 2 and 3). This outcome supports the mechanistic hypothesis that a less reducing photocatalyst and a less oxidizing electrophilic fluorine source could circumvent the deleterious chemoselectivity observed in our initial experiment. Moreover, replacing the (TMS)<sub>3</sub>SiH with supersilanol [(TMS)<sub>3</sub>SiOH] and employing K<sub>3</sub>PO<sub>4</sub> as base improved the overall efficiency for alkyl fluoride production to 87% yield (entry 5). Control experiments revealed that the reaction requires light and supersilanol (see SI for details);

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however, removal of the photocatalyst did not fully suppress product formation (entry 7, 22% yield), an unexpected finding that led us to question our initial mechanistic hypothesis. Intriguingly, further studies to evaluate an array of photocatalysts and photosensitizers (see SI for details) demonstrated that 2.5 mol% benzophenone provided the desired alkyl fluoride adduct in 86% yield (entry 8).

Given the success of benzophenone as a suitable replacement for the Ir photocatalyst, we next sought to examine the mechanistic aspects of this novel fluorination protocol. More specifically, we began to question if a photoinitiation-radical chain propagation pathway was operating. Such a mechanism would be consistent with the negligible absorbance of benzophenone within the range of visible light employed (see SI for details). Indeed, experiments to determine the quantum yield for this process revealed a value significantly higher than unity ( $\phi > 1000$ ), indicating that a radical propagation step is involved (see SI for details).

On the basis of the results above, a revised mechanistic description for the relevant fluorine atom transfer is presented in Scheme 1. Numerous radical initiation events may be operative in this system. The reaction proceeds, albeit in lower efficiency, in the absence of benzophenone (table 1, entry 7); thus, plausible initiation events may include the bond homolysis of a minute concentration of the weaker bonds in the system (e.g., C-Br and N-F). In the presence of benzophenone (1), irradiation with visible light should lead to a small concentration of the corresponding aryl ketone triplet excited state (2), which is known to serve as a potent hydrogen atom abstractor as well as a strong oxidant.<sup>17</sup> The excited benzophenone may engage the supersilanol in either a SET or HAT event to deliver a silvl radical (3) (see SI for details). Further investigations into the exact nature of this interaction are ongoing. Both silyl radical abstraction of alkyl bromides<sup>9</sup> (Scheme 1, XAT) as well as fluorine atom transfer from NFSI

to alkyl radicals<sup>14</sup> are known and well-precedented. The nitrogen-centered radical **5** formed can then undergo single electron transfer (SET) from supersilanol (or the corresponding silanolate), followed by a radical Brook rearrangement<sup>18</sup> to furnish a silyl radical species; alternatively, **5** can abstract a hydrogen-atom from the silanol O–H bond (see SI for details) to generate a silyl radical species following rearrangement.

To further explore the plausibility of our proposed radical chain pathway and to probe the unique selectivity observed, we performed a series of density functional theory (DFT) calculations (Figure 2). These computational studies using the supersilyl radical  $6^{19}$  revealed that the formation of the strong C-F and Si-O bonds provides a powerful thermodynamic driving force. Remarkably, the supersilyl radical exhibits excellent kinetic selectivity for the C-Br bond of the alkyl bromide over the weaker N-F bond of NFSI. While both of these steps are substantially exergonic (-17.6 kcal/mol and -64.8 kcal/mol, respectively), the N–F abstraction step proceeds with a less favorable activation free energy of 13.1 kcal/mol, which is 1.9 kcal/mol higher than that of the corresponding C-Br abstraction. Importantly, computational analysis reveals that this kinetic discrepancy is due to a sharper increase in the energy required to distort the less polarizable NFSI into its transition state geometry as compared to the alkyl bromide (see SI for details), in line with our initial theoretical considerations. Importantly, fluorine atom transfer from NFSI will lead to the corresponding nitrogen-centered radical (5) which is polarity matched to abstract a hydrogen atom from the hydridic silane 7, thereby propagating this mechanism via a supersilyl radical species. Details of this computational study, including DFT calculations for a variety of alternative or competing reaction pathways, are provided in the Supporting Information.

We next sought to investigate the generality of the kinetic selectivity by exploring the scope of this novel  $C(sp^3)$ -F bond-



**Figure 2.** DFT free energy profile (in kcals/mol) and calculated transition state structures for the proposed radical chain at the M06-2X/6-311++G(d,p)//M06-2X/6-31G(d) level of theory. Hydrogen atoms are omitted for clarity. Interatomic distances are in Ångströms.





<sup>*a*</sup>Yields of isolated products unless otherwise indicated. Performed with benzophenone (2.5 or 5 mol%), alkyl bromide (0.5 mmol), NFSI (3 equiv.), (TMS)<sub>3</sub>SiOH (1.75 equiv.), and base (K<sub>3</sub>PO<sub>4</sub> or Na<sub>2</sub>HPO<sub>4</sub>, 2 equiv.) in 1:1 MeCN/H<sub>2</sub>O for 1–8 h. See supporting information for experimental details. <sup>*b*</sup>Yields determined by <sup>19</sup>F NMR analysis (average of two runs). <sup>*c*</sup>Starting material d.r. = 8:1. <sup>*d*</sup>Concentration of 0.08 M.

forming reaction. As demonstrated in Table 2, a broad range of cyclic and acyclic secondary alkyl bromides are readily transformed to the corresponding alkyl fluorides in good to excellent yields. Specifically, a variety of ring sizes from 4- to 7-membered rings were well tolerated (**8–14**, 41–99% yield), including an array of saturated and unsaturated heterocycles. Notably, functionalities that are typically sensitive to nucleophilic fluorination conditions (e.g., DAST for deoxyfluorination), including benzylic alcohols and phenols, as well as substrates prone to elimination, were fully compatible with this open-shell mechanism (**15–18**, 62–83% yield). As one notable example,  $\beta$ -fluoroamine **18**, a motif found in numerous medicinal agents,<sup>1b</sup> was readily generated from the corresponding  $\beta$ -bromoamine (83% yield). To further illustrate the orthogonal nature of this transformation compared to closed-shell ionic mechanisms, we were delighted to find that

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<sup>*a*</sup>Yields of isolated products unless otherwise indicated. Performed with benzophenone (2.5 or 5 mol%), alkyl bromide (0.5 mmol), NFSI (3 equiv.), (TMS)<sub>3</sub>SiOH (1.75 equiv.), and base (K<sub>3</sub>PO<sub>4</sub> or Na<sub>2</sub>HPO<sub>4</sub>, 2 equiv.) in 1:1 MeCN/H<sub>2</sub>O for 1–8 h. See supporting information for experimental details. <sup>*b*</sup>Yields determined by <sup>19</sup>F NMR analysis (average of two runs).

an array of monosaccharides and nucleosides could be readily transformed to their  $\alpha$ -fluoro analogs without the requirement of accessing high-energy  $\beta$ -acetoxy- or  $\beta$ -fluoro-oxocarbenium ions (**19–21**, 85–90% yield).

Cyclic and acyclic tertiary fluorides, typically difficult to access using traditional bromide substitution mechanisms, were also successfully generated using this open-shell fluorination protocol (22–29, 55–86% yield). Importantly, aryl bromides and chlorides are comparatively unreactive towards abstraction, thereby enabling chemoselective fluorination of the attendant tertiary bromides (25 and 26, 82% and 63% yield, respectively). Moreover, the utility of this technology in comparison to nucleophilic deoxygenation mechanisms was further highlighted in that a range of carbonyl moieties were readily tolerated, including aldehydes, ketones, and esters (27, 22–23, 55–82% yield). In addition, primary and benzylic bromides could be converted to their corresponding fluorides, albeit in lower yields (28 and 29, 24% and 27% yield, respectively).<sup>20</sup> As a further demonstration of the utility of this new fluorination technology, we next examined the capacity to form geminal difluoroalkanes, a motif increasingly incorporated into medicinal agents. As shown in Table 3, the desired difluoride moiety was formed in excellent yield from the corresponding *gem*-dibromide using an iterative halogen-atom abstraction/radical capture mechanism (**30**, 72% yield). Given the accessibility of  $C(sp^3)$ -geminal dibromo systems,<sup>21</sup> we expect this dual-fluorination variant will find significant implementation in both academic and industrial settings.

### **Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: (link to DOI) Experimental procedures, spectral data, and details of the computational study

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# **Graphical TOC**



 

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