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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

ABSTRACT: We disclose a novel radical strategy for the fluorination of alkyl bromides via the merger of silyl radical-mediated 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.[1−34] 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^3)−F bonds include deoxyfluorination of alcohols, hydrofluorination of alkenes, decarboxylative fluorination of acids, and radical C−H fluorination. 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.[5−7]

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.[8] 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

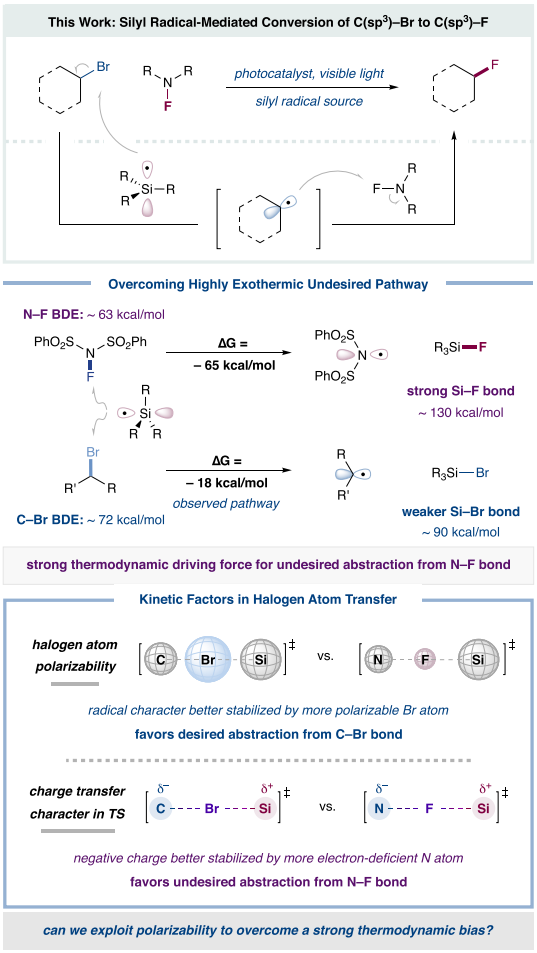

Figure 1. Silyl radical-mediated fluorination of alkyl bromides.

metallaphotoredox reaction designs, including nickel- and copper-catalyzed cross-couplings of value to the medicinal chemistry sector.[9] With these technologies in mind, and given 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

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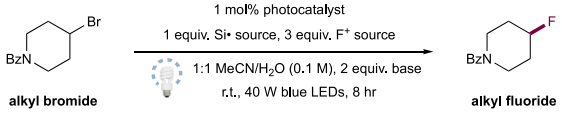
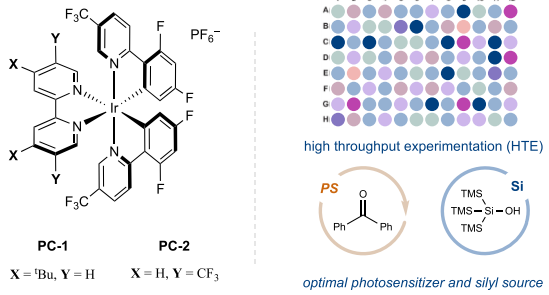
Table 1. Optimization of Silyl Radical-Mediated Fluorination

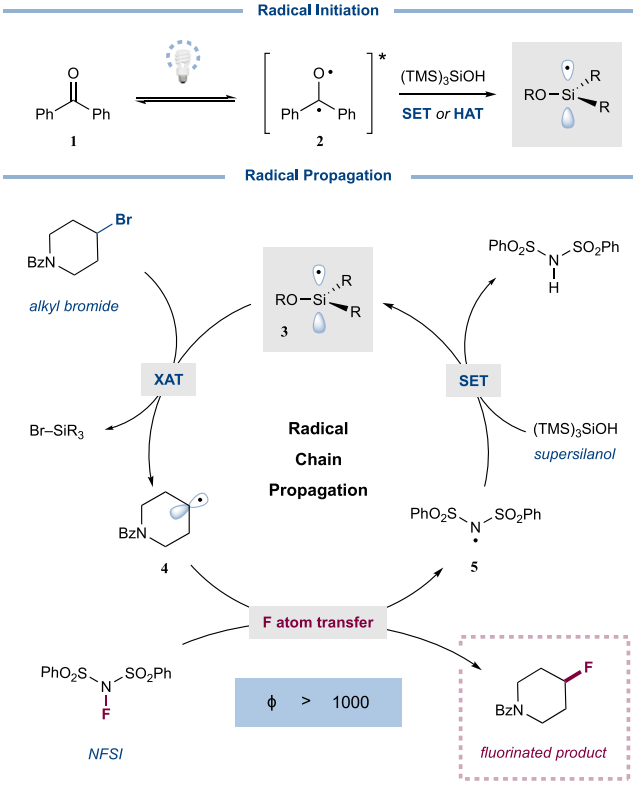


entry	photocatalyst	Si• source	F+ source	base	yield
1	**PC-1**	$(TMS)_3SiH$	Selectfluor	Na_2HPO_4	1%
2	**PC-1**	$(TMS)_3SiH$	NFSI	Na_2HPO_4	31%
3	**PC-2**	$(TMS)_3SiH$	NFSI	Na_2HPO_4	46%
4	**PC-2**	$(TMS)_3SiOH$[a]	NFSI	Na_2HPO_4	76%
5	**PC-2**	$(TMS)_3SiOH$[b]	NFSI	K_3PO_4	87%
6	**PC-2**	$(TMS)_3SiOH$[b]	NFSI	none	49%
7	none	$(TMS)_3SiOH$[b]	NFSI	K_3PO_4	22%
8	benzophenone[c]	$(TMS)_3SiOH$[b]	NFSI	K_3PO_4	86%



[a]1.5 equiv. [b]1.75 equiv. [c]2.5 mol%.

Scheme 1. Proposed Radical Chain Initiation and Propagation



a mild fluorinating agent. Notably, an open-shell fluorination strategy should provide complementary scope to classical substitution methods. While an open-shell fluorination strategy has been developed for tertiary alkyl bromides,[7] 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 a 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)[10] versus formation of the weaker Si−Br bond via desired abstraction from the alkyl bromide C−Br bond (∼70 kcal/mol).[11] 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 silicon-centered radical[12] can be better stabilized by the electron-deficient 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,[13] 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 (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 silyl radical generation[9] and fluorine-atom transfer[14,15] 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 $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (**PC-1**), tris(trimethylsilyl)silane $[(TMS)_3SiH]$ as the silyl radical agent, Selectfluor as the fluorine source, along with Na_2HPO_4 in $MeCN/H_2O$. Despite the potential challenges of this approach, we observed 1% of the desired fluoroalkyl adduct (Table 1, entry 1), presumably due to photocatalytic reduction ($E_{1/2}^{red}[Ir^{III}/Ir^{II}]$ = −1.37 V vs SCE in MeCN)[9] of the electrophilic fluorine source (Selectfluor, E_{pc} = +0.33 V vs SCE in MeCN)[15] 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)[14] in combination with the photocatalyst **PC-2**, $[Ir(dF(CF_3)ppy)_2((5,5'\text{-}CF_3)bpy)]PF_6$ ($E_{1/2}^{red}[Ir^{IV}/Ir^{III}]$ = −0.42 V vs SCE in MeCN)[16] (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 $(TMS)_3SiH$ with supersilanol $[(TMS)_3SiOH]$ and employing K_3PO_4 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 Supporting Information for details); however, removal of the photocatalyst did not fully suppress

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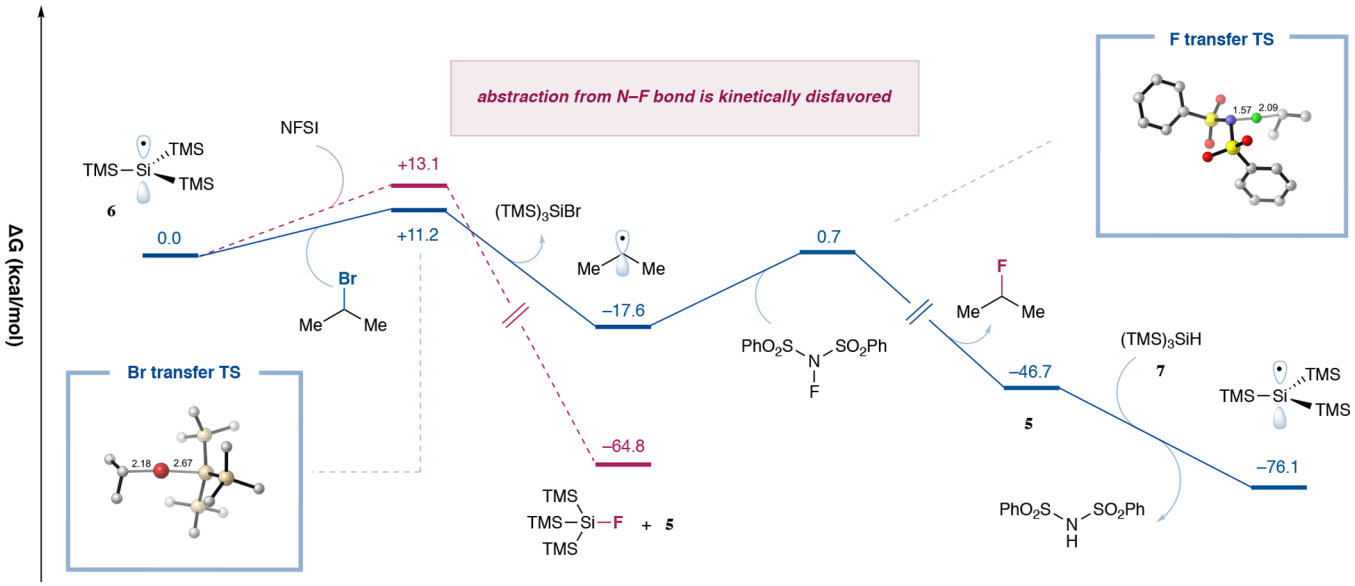

Figure 2. DFT free energy profile (in kcals/mol) and calculated transition state structures for the proposed radical chain at the M06-2X/6-311++G(d,p)//M06-2X/6-31G(d) level of theory. Hydrogen atoms are omitted for clarity. Interatomic distances are in Ångströms.

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 Supporting Information 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 Supporting Information for details). Indeed, experiments to determine the quantum yield for this process revealed a value significantly higher than unity (φ > 1000), indicating that a radical propagation step is involved (see Supporting Information 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.[17] The excited benzophenone may engage the supersilanol in either a SET or HAT event to deliver a silyl radical (**3**) (see Supporting Information for details). Further investigations into the exact nature of this interaction are ongoing. Both silyl radical abstraction of alkyl bromides[9] (Scheme 1, XAT) as well as fluorine-atom transfer from NFSI to alkyl radicals[14] 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[18] to furnish a silyl radical species; alternatively, **5** can abstract a hydrogen atom from the silanol O−H bond (see Supporting Information 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 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 Supporting Information 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 investigated the generality of the kinetic selectivity by exploring the scope of this novel C(sp^3)−F bond-forming reaction. As demonstrated in Table 2, a broad range of cyclic and acyclic secondary alkyl bromides is 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

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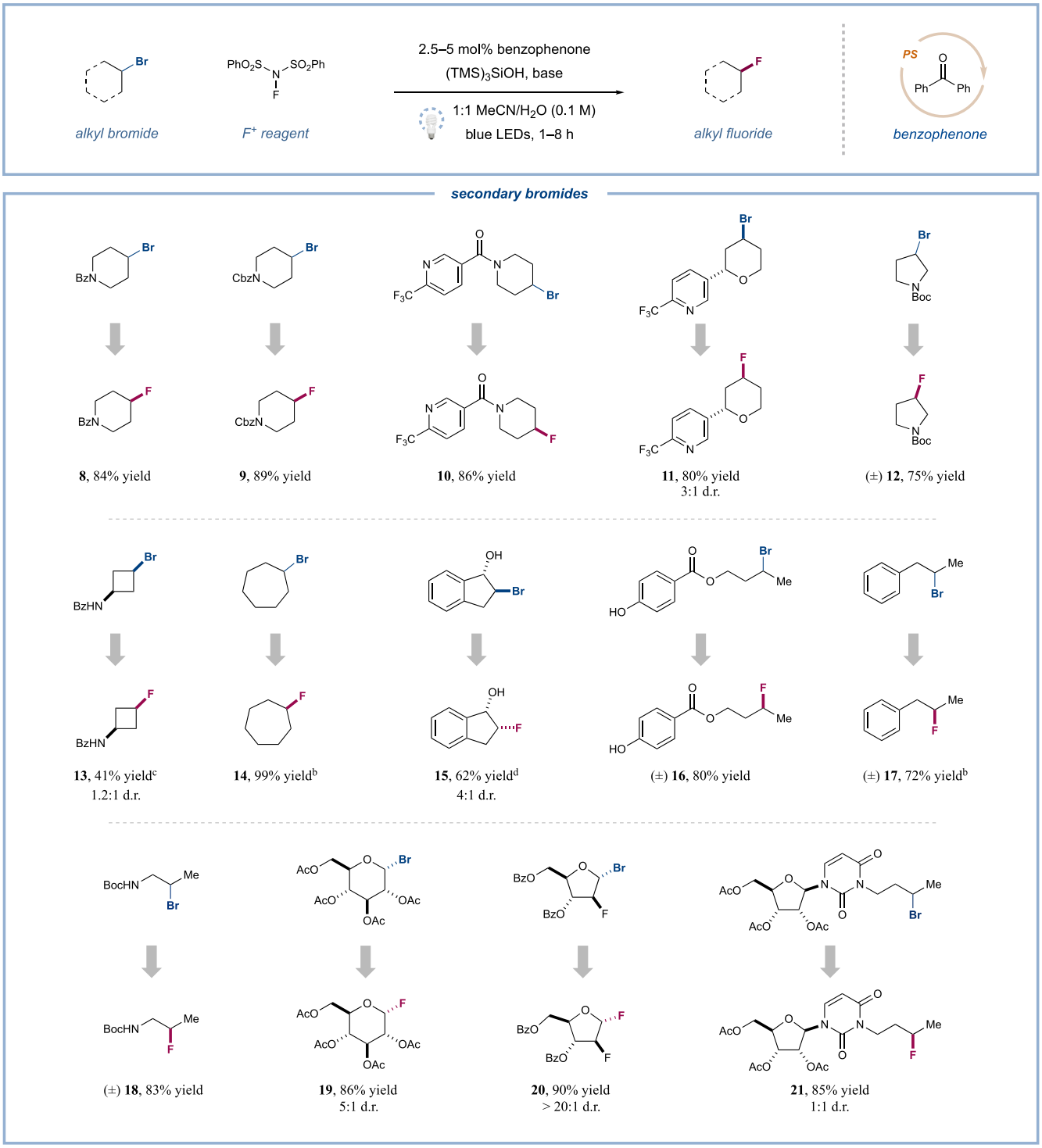
Table 2. Scope for the Transition-Metal-Free, Silyl Radical-Mediated Protocol for the Fluorination of Secondary Alkyl Bromides[a]



[a]Yields of isolated products unless otherwise indicated. Performed with benzophenone (2.5 or 5 mol %), alkyl bromide (0.5 mmol), NFSI (3 equiv), $(TMS)_3SiOH$ (1.75 equiv), and base (K_3PO_4 or Na_2HPO_4, 2 equiv) in 1:1 $MeCN/H_2O$ for 1−8 h. See Supporting Information for experimental details. [b]Yields determined by ^{19}F NMR analysis (average of two runs). [c]Starting material d.r. = 8:1. [d]Concentration of 0.08 M.

compatible with this open-shell mechanism (**15**−**18**, 62−83% yield). As one notable example, β-fluoroamine **18**, a motif found in numerous medicinal agents,[1b] was readily generated from the corresponding β-bromoamine (83% yield). To further illustrate the orthogonal nature of this transformation compared to closed-shell ionic mechanisms, we were delighted to find that an array of monosaccharides and nucleosides could be readily transformed to their α-fluoro analogues without the requirement of accessing high-energy β-acetoxy- or β-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

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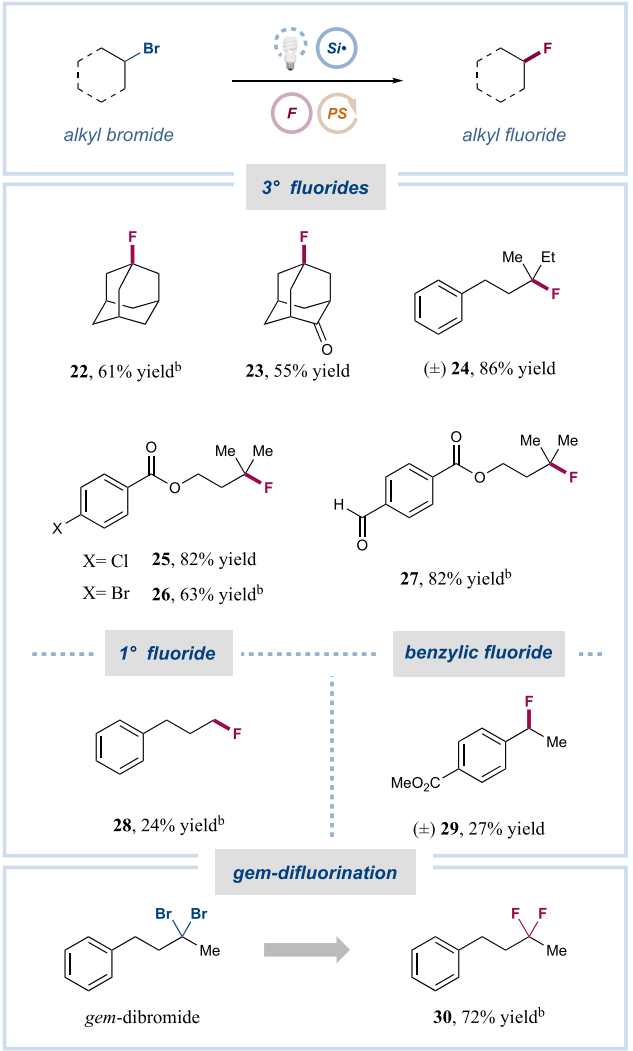
chlorides are comparatively unreactive toward abstraction, thereby enabling chemoselective fluorination of the attendant tertiary bromides (**25** and **26**, 82 and 63% yield, respectively). Moreover, the utility of this technology in comparison to nucleophilic deoxygenation mechanisms was further highlighted in that a range of carbonyl moieties was 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).[20]

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,[21] we expect this dual-fluorination variant will find significant implementation in both academic and industrial settings.

Table 3. Further Scope of Fluorination of Alkyl Bromides[a]



[a]Yields of isolated products unless otherwise indicated. Performed with benzophenone (2.5 or 5 mol %), alkyl bromide (0.5 mmol), NFSI (3 equiv), $(TMS)_3SiOH$ (1.75 equiv), and base (K_3PO_4 or Na_2HPO_4, 2 equiv) in 1:1 MeCN/H_2O for 1–8 h. See Supporting Information for experimental details. [b]Yields determined by ^{19}F NMR analysis (average of two runs).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.9b11434.

Experimental procedures, spectral data, and details of the computational study (PDF)

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Notes

The authors declare no competing financial interest.

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