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Potassium Alkylpentafluorosilicates, Primary Alkyl Radical Precursors in the C-1 Alkylation of Tetrahydroisoquinolines

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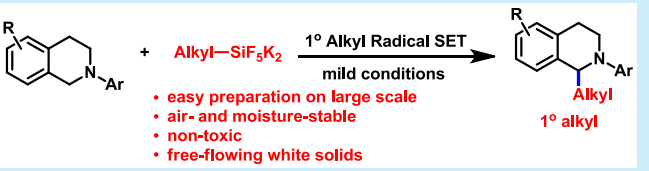
Supporting Information

ABSTRACT: In this study, we demonstrate that potassium alkylpentafluorosilicates ($RSiF_5K_2$) are efficient primary alkyl radical precursors for selective $C(sp^3)-C(sp^3)$ bond-forming reactions. $RSiF_5K_2$ reagents are white, free-flowing solids and are moisture and air stable. This class of reagents enables the direct C-1 alkylation of tetrahydroisoquinolines under mild conditions via single-electron transfer. The broad substrate scope of both alkylpentafluorosilicates and tetrahydroisoquinolines is tolerated in this transformation. Both radical scavenger and EPR capture experiments show that the primary radical is generated by the oxidation of $RSiF_5K_2$. A mechanism involving alkyl radical addition to an iminium salt followed by reduction by an amine is proposed.



Free radical couplings that proceed via single-electron transfer (SET) under metal-mediated redox conditions[1] or photoredox catalysis[2] have emerged as a uniquely effective mode of reactivity for selective $C(sp^2)-C(sp^3)$ bond formation in synthetic chemistry. However, the radical intermediates in such processes and their corresponding precursors are limited mainly to secondary and tertiary C-centered alkyl variants. This is due to the fact that the precursors have lower disassociation energy and the radical intermediates have inherently higher stability than in the case of primary variants. Though some classical organometallic compounds, such as organotins and organolithiums, and more recently developed progenitors, including organoborons,[3] peroxides,[4] carboxylic acids and their derivatives,[5] alkyl halides,[6] and others,[7] can be readily converted into primary alkyl radicals, some of them require special substitution patterns to stabilize the corresponding radical, and some of these approaches also lack functional group tolerance. There is high demand for developing practical precursors for primary C-centered radicals. In parallel, achieving controllable transformations with primary alkyl radicals, such as $C(sp^3)-C(sp^3)$ coupling, is also a pertinent challenge.

To this end, the Molander and Fensterbank laboratories have recently reported that primary alkyl hypervalent silicates are efficient C-based radical precursors.[8] In their preliminary reports, primary alkyl radicals were successfully generated from the stabilized bis(catecholato)silicates under photoredox conditions with Ir or Ru catalysts (Scheme. 1a). The resulting primary alkyl radicals were then demonstrated to be competent in $C(sp^2)-C(sp^3)$ bond-forming reactions, such as addition to alkenes, and cross-coupling with vinyl halides or aryl bromides, as well as viable initiators for the cross-coupling of thiols and aryl bromides.

Inspired by these reports, we envisioned that alternative hypervalent silicate radical precursor that are atom-economic, environmentally friendly, nontoxic, simple to prepare, and convenient to handle would broaden the utility of such reagents in the synthesis of C−C bonds, especially in the construction of $C(sp^3)-C(sp^3)$ bonds. To achieve this goal, we focused on potassium alkylpentafluorosilicates ($RSiF_5K_2$). Though Kumada and others have previously observed the generation of carbon-centered radicals from $RSiF_5K_2$ upon treatment with stoichiometric quantities of $Cu^{II}X_2$, halogens, or NBS, these primary

Scheme 1. Hypervalent silicates as radical precursors

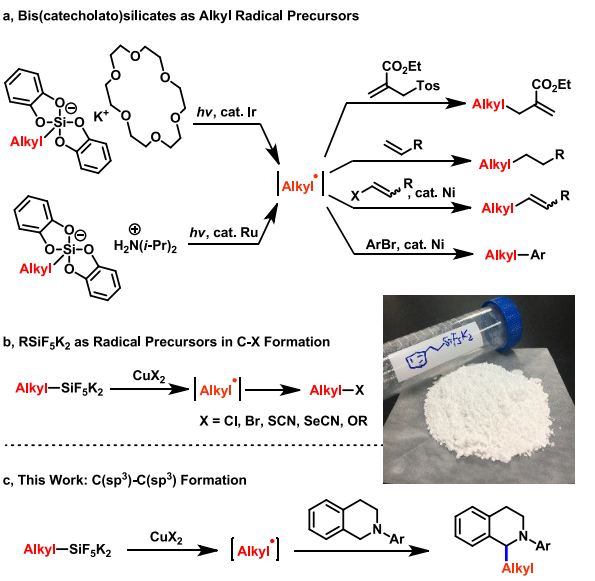


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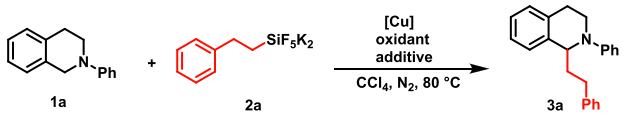
Table 1. Optimization of the Reaction Conditions[a]



entry	[Cu]	oxidant	PTC	additive	base	solvent	yield[b] (%)
1		TBHP (aq)				DCE	0
2	CuBr	TBHP (aq)				DCE	>5 (2)
3	CuBr	DTBP				CCl_4	39
4	CuBr	DTBP	TBAI			CCl_4	67
5	CuBr	DTBP	TBAF			CCl_4	66
6	$Cu(OTf)_2$		TBAF			CCl_4	0
7	$Cu(OTf)_2$		TBAF	Et_3N		CCl_4	63
8	$CuCl_2$		TBAF	Et_3N		CCl_4	46
9	$Cu(OTf)_2$		TBAF	Et_2NH		CCl_4	65
10	$Cu(OTf)_2$		TBAF	$tBuNH_2$		CCl_4	52
11	$Cu(OTf)_2$		TBAF	Et_2NH	NaOAc	CCl_4	52
12	$Cu(OTf)_2$		TBAF	Et_2NH	$NaOAc{\cdot}3H_2O$	CCl_4	69
13	$Cu(OTf)_2$		TBAF	Et_2NH	$KHCO_3$	CCl_4	72 (67)
14[c]	$Cu(OTf)_2$		TBAF	Et_2NH, H_2O	$KHCO_3$	CCl_4	88 (82)

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (1.2 mmol), oxidant (2.2 equiv), TBAF (10 mol %), base (2 equiv), additive (3 equiv), CCl_4 (2 mL), 80 °C, N_2. [b]Yields were determined by ^1H NMR spectra of crude reaction mixtures with Ph_3CH as internal standard. Isolated yields are in parentheses. [c]H_2O (3 equiv) was added.

radicals could only be trapped by a few select reaction partners, including the counteranions of the Cu^{II} salts, alcoholic solvents, or actived alkenes, in reasonable yields (Scheme 1b).[9] Methods that utilize primary alkyl radicals generated from $RSiF_5K_2$ precursors in selective $C(sp^3)-C(sp^3)$ bond formation are rare.[10]

We further envisioned that such species would be well-suited for traditionally challenging $C(sp^3)-H$ functionalization for $C(sp^3)-C(sp^3)$ bond formation[11] in a catalytic cycle in which a tertiary amine is oxidized to the corresponding iminium salts followed by primary radical addition.[12] Herein, we report a Cu(II)-mediated coupling of *N*-aryl tetrahydroisoquinolines at the C−1 position with $RSiF_5K_2$, forming $C(sp^3)-C(sp^3)$ bonds under mild conditions *via* SET (Scheme. 1c). In this reaction, alkyl pentafluorosilicates ($RSiF_5K_2$) are demonstrated to be efficient primary C-centered radical precursors.

We initiated our study by investigating the reaction of *N*-phenyl tetrahydroisoquinoline (**1a**) with potassium phenethylpentafluorosilicate (**2a**). Encouragingly, the desired product **3a** was obtained in the presence of 30 mol % CuBr and 2 equiv of TBHP (5.5 M in decane) in anhydrous dichloromethane under N_2 atmosphere for 11 h, albeit only in 2% isolated yield (Table 1, entry 2). When we switched to CCl_4 as solvent and DTBP as oxidant, 39% conversion was observed (entry 3). Increasing CuBr to 50 mol % catalyst loading and using 3 equiv of oxidant further improved the conversion (entry 4). Phosphine- or pyridine-type ligands, which are generally used to promote Cu-catalyzed reactions, inhibited this transformation. When a phase-transfer reagent was introduced to the reaction mixture, the yield increased. TBAF afforded 66% yield of **3a** after 8 h at 80 °C (entry 5); however, the reaction was contaminated with trace quantities of a byproduct that resulted from the coupling of the *tert*-butoxyl radical (from oxidant DTBP, di-*tert*-butyl peroxide) with **1a** at the C-1 position. This observation prompted us to consider the use of stoichiometric Cu(II) as oxidant. Use of 2.2 equiv of $Cu(OTf)_2$ alone did not afford any desired product (Table 1, entry 6). After considering the mechanistic features of the reaction (vide infra), we realized that single-electron reductants, such as amines, were necessary for reducing the intermediate to the final product.[13] Thus, diethylamine was identified as a suitable additive, and the desired product was achieved in 69% yield (Table 1, entry 12). Various copper salts were screened, among which $Cu(OTf)_2$ was found to be the most efficient. Interestingly, we found that the addition of inorganic base and H_2O could further improve the transformation; thus, $KHCO_3$ and 3 equiv of H_2O together provided 82% isolated yield (Table 1, entries 11−13). A plausible explanation is that water might promote the transformation or simply increase the solubility of the silicate salts in the reaction, and a similar water effect has also observed for potassium organotrifluoroborates (RBF_3K).[14]

Having identified the optimal conditions, we next examined the substrate scope of organopentafluorosilicate reagents as primary radical precursors using *N*-phenyl tetrahydroisoquinoline (**1a**) (Table 2) as a model substrate. First, the reactivity of various phenethyl pentafluorosilicates was tested (**2a**−**2h**). We found that these pentafluorosilicates reacted smoothly with **1a** to provide the desired alkylation products in moderate to good yields (**3a**−**3h**, respectively). In all of these cases, the products resulted exclusively from 2-phenethyl radical addition to **1a**, with no evidence of formation of the corresponding 1-phenethyl (i.e., benzyl)-substituted products.[15] Multiple functional groups on the aryl ring of the phenethylsilicates, such as Me (**3b**), OMe (**3c**, and **3d**), halogens F, Cl, Br, (**3e**−**3g**), and ester (**3h**), were compatible with the mild reaction conditions and afforded the $C(sp^3)-C(sp^3)$-coupled products in good yields. These functional groups provide an additional handle for further synthetic elaboration. Additionally, benzyl pentafluorosilicates (**2i**−**2k**) that contain substituents are also compatible for this $C(sp^3)-C(sp^3)$ bond-forming reaction, providing the desired products in moderate yields (**3i**−**3k**). Furthermore, 3-phenylpropyl silicate (**2l**) reacted readily with **1a** to provide the desired product (**3l**) in moderate yield. At last, we examined the compatibility of purely aliphatic pentafluorosilicates in this transformation. It turned out that ethyl, 2-carbonylhexyl, ethoxymethyl, and glycomethyl petafluorosilicates reacted successfully with the

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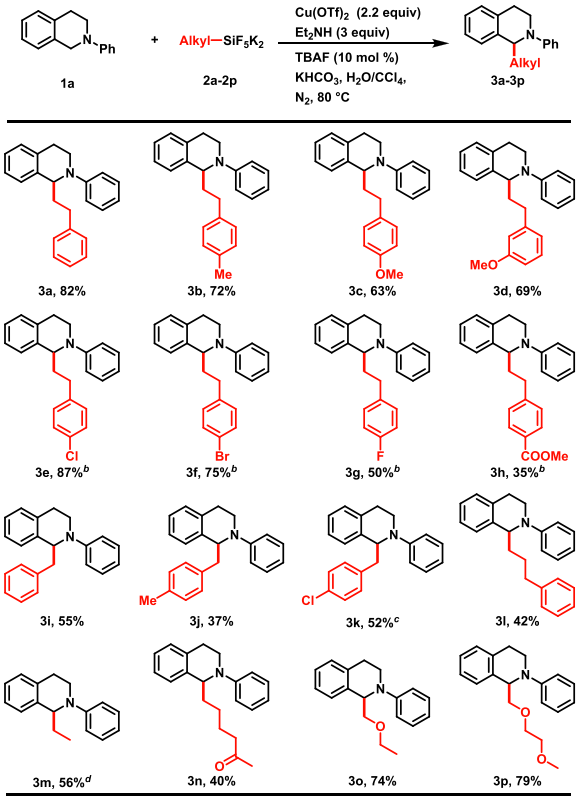
Table 2. Scope of Organopentafluorosilicates[a]



[a]Reaction conditions: **1a** (0.3 mmol), **2** (1.2 mmol), $Cu(OTf)_2$ (0.66 mmol), TBAF (0.03 mmol), Et_2NH (0.9 mmol), $KHCO_3$ (0.6 mmol), H_2O (0.9 mmol), CCl_4 (2 mL), N_2, 80 °C, 8 h. [b]Air, 60 °C, 36 h. [c]60 °C, 36 h. [d]Air, 60 °C, 12 h.

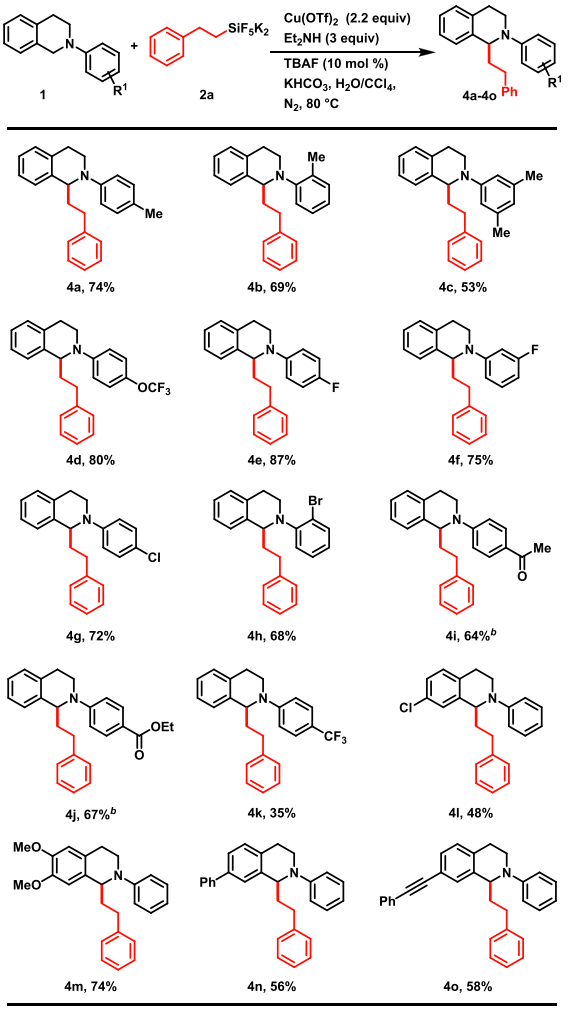
isoquinonline substrate and delivered the desired $C(sp^3)-C(sp^3)$ cross-coupled products in moderate to good yields (**3m–3p**). These examples show that organopentafluorosilicate reagents are reliable precursors for generating the corresponding C-centered primary radicals.

We next probed the scope of tetrahydroisoquinolines (**1**) with potassium phenethylpentafluorosilicates (**2a**) (Table 3). A variety of *N*-aryl tetrahydroisoquinoline substrates (**1b–1p**) reacted smoothly with **2a** to afford $C(sp^3)-C(sp^3)$ cross-coupled products in moderate to good yields. Substrates bearing substituents on the *N*-aryl ring, including methyl (**4a–4c**), trifluoromethoxyl (**4d**), halogens such as fluoro (**4e**, and **4f**), chloro (**4g**), and bromo (**4h**), carbonyl (**4i**), and esters (**4j**), afforded the desired products in good yields. A strongly electron-withdrawing group, namely CF_3, is also tolerated (**4k**), albeit in low yield. Substituents on the tetrahydroisoquinoline ring, such as chloro (**4l**), methoxyl (**4m**), phenyl (**4n**), and alkynyl (**4o**), were well tolerated in the reaction, providing moderate to good yields (**4l–4o**).

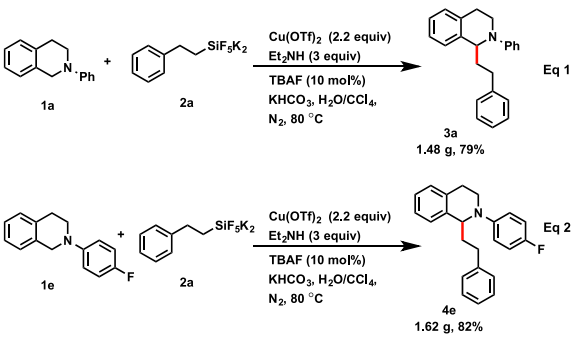
This protocol is good for gram-scale uses. For example, the reaction of 1.2 g of **1a** (6 mmol) with **2a** affords 1.48 g of **3a** in 79% yield (eq 1). Similarly, the reaction between 1.37 g of **1e** and **2a** affords 1.62 g of the desired product, **4e**, in 82% isolated yield (eq 2).

To understand the reaction mechanism, a radical scavenger test was conducted. When pentafluorosilicate **2a** was stirred with 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO) in the presence of catalytic $CuBr_2$ and 3 equiv of di-*tert*-butyl peroxide (DTBP) in THF at 80 °C, we isolated 55% yield of 2,2,6,6-

Table 3. Scope of *N*-Phenyl Tetrahydroisoquinolines[a]



[a]Reaction conditions: **1a** (0.3 mmol), **2** (1.2 mmol), $Cu(OTf)_2$ (0.66 mmol), TBAF (0.03 mmol), Et_2NH (0.9 mmol), $KHCO_3$ (0.6 mmol), H_2O (0.9 mmol), CCl_4 (2 mL), N_2, 80 °C, 8 h. [b]The organopentafluorosilicate was added in two batches.



tetramethyl-1-phenethoxypiperidine **5** (eq 3). Moreover, under analogous conditions, **2a** was found to undergo Minisci-type C2-alkylation of a representative pyridine substrate (eq 4). These results are consistent with a mechanism in which the alkyl pentafluorosilicate serves as a C-centered radical precursor in the coupling reaction.

To gain more insight into the redox chemistry involved in this reaction, we next performed EPR capture experiments. When **2a**, $Cu(OTf)_2$, and phenyl *tert*-butyl nitrone (PBN, a spin-trapping

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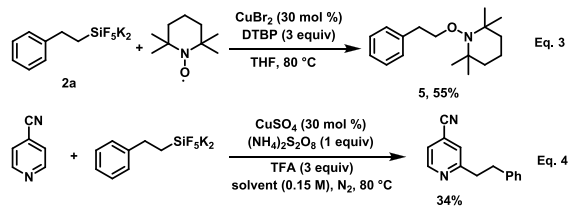

reagent) were stirred in CCl_4 at 80 °C for 2 h, the EPR signal clearly indicated formation of a PBN adduct, R(Ph)CHN-(•OC)^{t}Bu (Figure 1a, red line), in which g = 2.00632, α_N = 13.98G, and α_H = 1.69G. However, in the control experiment (i.e., in the absence of **2a**), no radical adduct was observed (Figure 1a, black line). It should be noted that the R group in the spin-adduct product, R(Ph)CHN(•OC)^{t}Bu, may be two different groups. One possibility is the phenethyl moiety, as would be expected from radical generation via oxidation of $RSiF_5K_2$ by Cu^{II}. The other possibility would result from addition of $•CCl_3$ radical that is generated from the Cl abstraction of CCl_4 by the phenethyl radical.[16] Next, we added PBN under the standard reaction conditions, and in this case, we observed a similar alkyl radical spin adduct (Figure 1b) for which

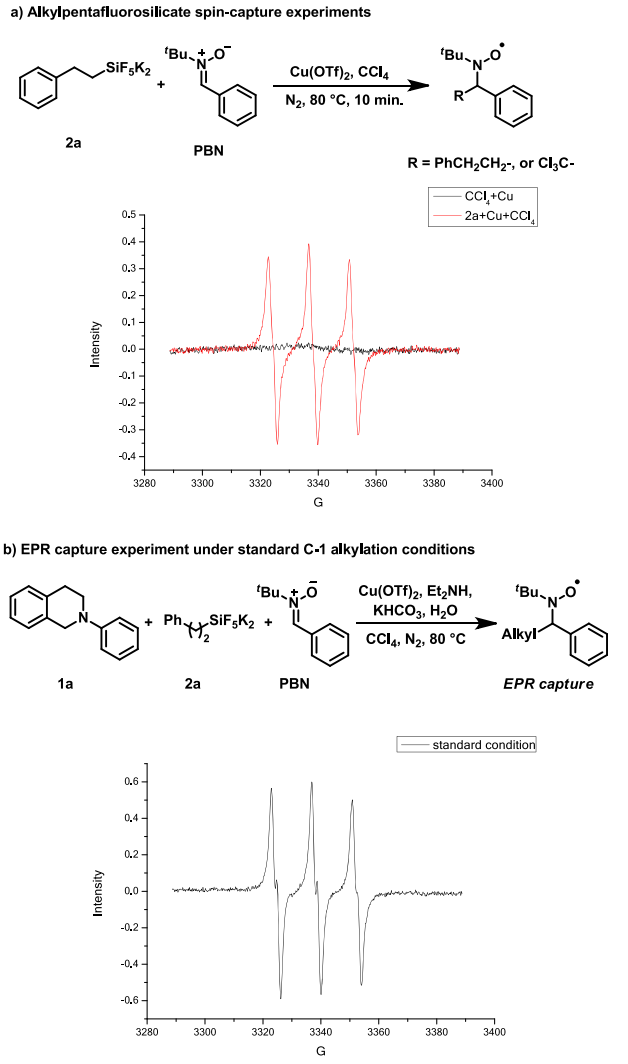

Figure 1. EPR capture tests. (a) EPR test for the alkyl pentafluorosilicate. (b) EPR test for the C-1 alkylation reaction mixture.

g = 2.00636, α_N = 13.90G, and α_H = 1.78G. Taking these results together, we can conclude that a C-centered primary free radical is involved in the reaction. This radical then plays an important role in C-1-selective C(sp^3)−C(sp^3) bond formation.[17]

Though elucidating the full mechanistic details remains the goal of ongoing investigations, based on the preliminary observations above, we propose a radical SET pathway for this transformation (Figure 2). Tetrahydroisoquinoline is oxidized

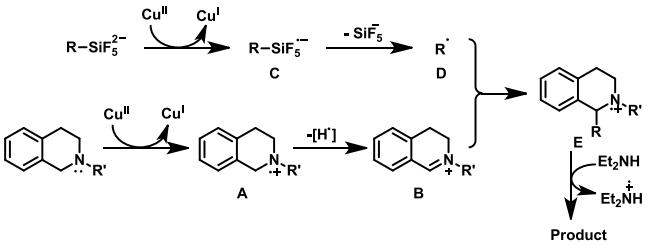

Figure 2. Proposed reaction mechanism.

by Cu(II) to provide radical cation **A**,[18] which then affords iminium salt **B** through homolytic hydrogen-atom abstraction.[19] The organopentafluorosilicate is oxidized by Cu(II) via SET to provide silicon-centered radical **C**,[20] which affords carbon-centered alkyl radical **D** by releasing SiF_5^- or SiF_4; attack of carbon-centered radical **D** on to the iminium ion **B** provides radical cation **E**, which is then reduced with an electron from diethyl amine to provide the final product.

In conclusion, we show that potassium alkylpentafluorosilicates ($RSiF_5K_2$) are an effective class of precursors for generating carbon-centered primary alkyl free radicals under mild oxidative conditions using stoichiometric copper(II). The resultant primary alkyl radical can be effectively trapped by an imium ion generated from *N*-phenyl tetrahydroisoquinoline at the C−1 position to afford a C(sp^3)−C(sp^3) cross-coupled product in moderate to good yields. We also trapped the primary radicals with a radical scavenger and performed EPR experiment to support the involvement of a radical intermediate. Organopentafluorosilicates are easily prepared on large scale, and they are generally air- and moisture-stable, nontoxic, free-flowing white solids, making them a valuable addition to the toolkit of primary alkyl radical precursors in synthetic chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01124.

Experimental procedures, and characterization data and spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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