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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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δ-C−H Mono- and Dihalogenation of Alcohols

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Cite This: J. Am. Chem. Soc. 2020, 142, 2766−2770

ABSTRACT: Alkoxy radicals have long been known to enable remote C−H functionalization via 1,5-hydrogen atom abstraction. However, methods for their generation traditionally have relied upon highly oxidizing metals, ultraviolet radiation, or preformed peroxide intermediates, which has prevented the development of many desirable transformations. Herein we report a new bench-stable precursor that decomposes to free alkoxy radicals via a previously unreported single-electron oxidation pathway. This new precursor enables the fluorination and chlorination of remote C−H bonds under exceptionally mild conditions with exceedingly high monoselectivity. Iterative use of this precursor enables the introduction of a second halogen atom, granting access to remote dihalide motifs, including CF_2 and CFCl.

The development of new chemical reactions to functionalize inert C−H bonds holds great promise in organic chemistry. Directed metalation has been extensively exploited to functionalize sp^3 C−H bonds in the past decade.[1−3] However, this process remains largely limited to C−H bonds that are three bonds away from the directing atom because of the preferential formation of five-membered metallacycles. While the development of ligands and directing groups to favor more distal C−H palladation has been recently demonstrated,[4] heteroatom-centered free radicals provide a potentially powerful alternative means to access these more remote C−H bonds via the process of 1,5-hydrogen atom transfer (HAT),[5] the Hofmann−Löffler−Freytag and Barton nitrite ester reactions being early examples of such reactions.

In light of our lab's previous efforts in remote radical C−H halogenation reactions via nitrogen-centered radicals,[6,7] we became interested in using alkoxy radicals to accomplish the remote C−H halogenation of alcohols. Hydrogen atom transfer reactions of alkoxy radicals to produce remotely functionalized alcohols are particularly desirable because of the prevalence of alcohols in natural products and drug targets. However, existing methods to accomplish the remote halogenation of alcohols pose practical limitations (Scheme 1A),[8−12] since alkoxy radicals are typically generated using stoichiometric organotin[13] or lead[14] reagents, hypervalent iodine,[15] or unstable precursors,[8−12] which are often not compatible with a variety of desirable transformations.

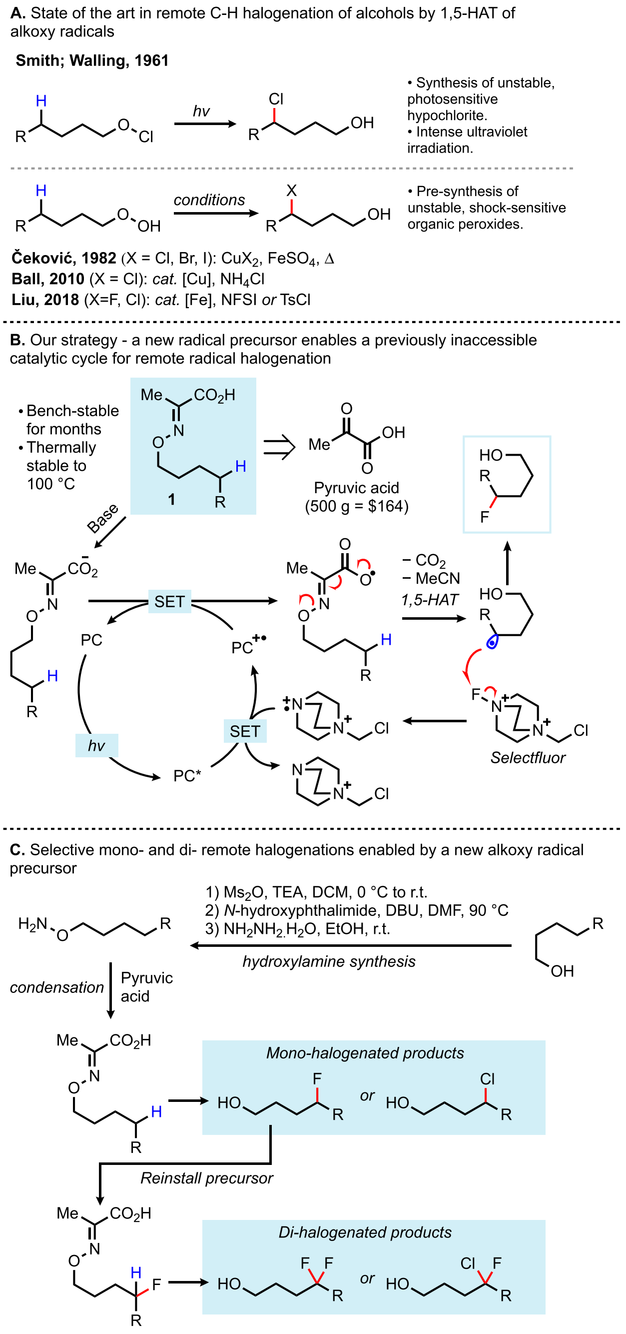
In this context, photoredox chemistry has furnished new means to generate heteroatom-centered radical intermediates from a range of convenient synthetic precursors.[16−18] These precursors undergo either a one-electron oxidation or reduction in the presence of a photoredox catalyst and subsequently decompose to yield the heteroatom-centered radical. In our efforts to develop alcohol-directed δ-C−H halogenation, several examples of visible-light-mediated alkoxy radical generation caught our attention.[18−26] However, since common electrophilic halogenation reagents such as Selectfluor and N-chlorosuccinimide (NCS) are quenched by single-electron reduction following halogen atom transfer, many of the previously reported alkoxy radical precursors, which decompose by single-electron reduction (e.g., N-alkoxyphthalimides[19−21] and N-alkoxypyridinium salts[22,25,26]), are unsuitable for a redox-neutral cycle. Thus, for a redox-neutral photoredox cycle to be feasible with the desired halogenation reagents, the alkoxy radical must be generated via single-electron oxidation of the precursor. In certain cases, oxidative pathways have been used to directly generate alkoxy radicals from free alcohols using either cerium catalysis[23] or proton-coupled electron transfer (PCET);[27,28] however, the narrow redox window of these cerium catalysts has limited their application to new transformations, while 1,5-HAT reactions of PCET-generated alkoxy radicals remain unreported. In order to overcome these limitations, we embarked on the development of a new alkoxy radical precursor with appropriate redox properties to enable remote alcohol C−H halogenation.

Therefore, drawing inspiration from previously reported decarboxylating precursors designed for nitrogen-centered radical HAT,[29,30] we questioned whether the alcohol-derived oxyimino acid directing group **1** recently reported by our lab[4] for palladium-catalyzed C−H activation might serve as the required alkoxy radical precursor. One-electron oxidation of the deprotonated directing group could initiate a decarboxylative sequence to yield carbon dioxide, acetonitrile, and an alkoxy radical competent for hydrogen atom abstraction (Scheme 1B[31]). Moreover, this directing group is easily prepared in a one-step condensation from the corresponding hydroxylamine using pyruvic acid, an inexpensive natural product.

Received: December 6, 2019
Published: January 30, 2020

https://dx.doi.org/10.1021/jacs.9b13171
J. Am. Chem. Soc. 2020, 142, 2766−2770

Scheme 1

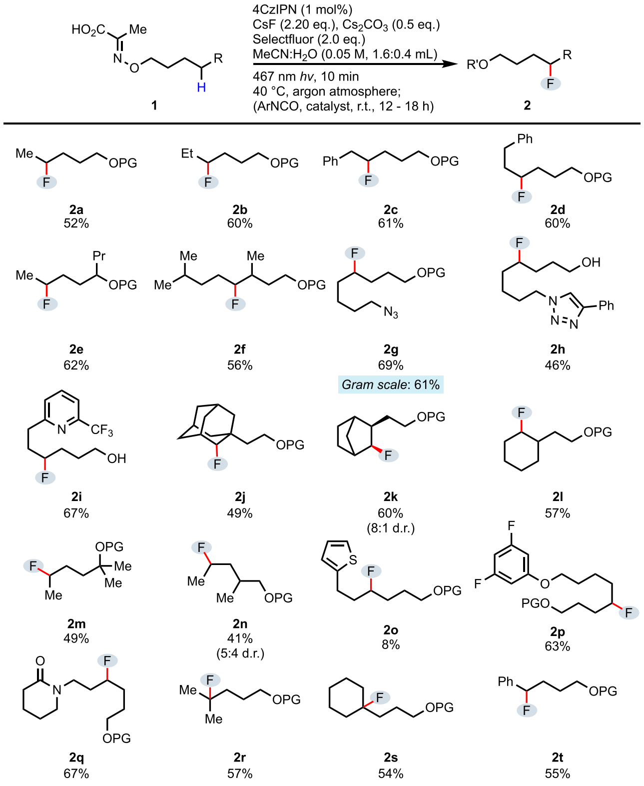


To accomplish this oxidation, we tested a range of photocatalysts possessing different excited-state redox potentials using irradiation with 467 nm light. When Selectfluor was used as a radical trapping reagent,[30,32,33] imino acid **1i** underwent decarboxylation and intramolecular HAT to provide a remotely generated carbon radical that was trapped to forge a carbon−fluorine bond. The choice of base was crucial to the success of this reaction, with a combination of cesium fluoride and cesium carbonate providing the product **2i** in 67% yield (see the Supporting Information (SI) for details)—we attribute the effectiveness of this base combination to fine-tuning of the pH of the reaction in the acetonitrile/water mixed solvent system. Notably, the organic photosensitizer (4s,6s)-2,4,5,6-tetra(9*H*-carbazol-9-yl)-isophthalonitrile (4CzIPN)[34] could supplant the expensive iridium complexes typically reported for decarboxylation reactions.[33] Control experiments conducted in the absence of photocatalyst and in the absence of light concluded that both light and the photocatalyst were crucial to the reaction's success.

Building on the success of this fluorination reaction, we questioned whether remote C−H chlorination might also be achieved. With NCS as the chlorine atom source and cesium carbonate as the base in acetonitrile as solvent, the desired remotely chlorinated product **3i** was obtained in 22% yield. Switching to ethyl trichloroacetate (ETCA) as the chlorine atom source, as recently disclosed by Reisman,[35] improved the yield to 63%.

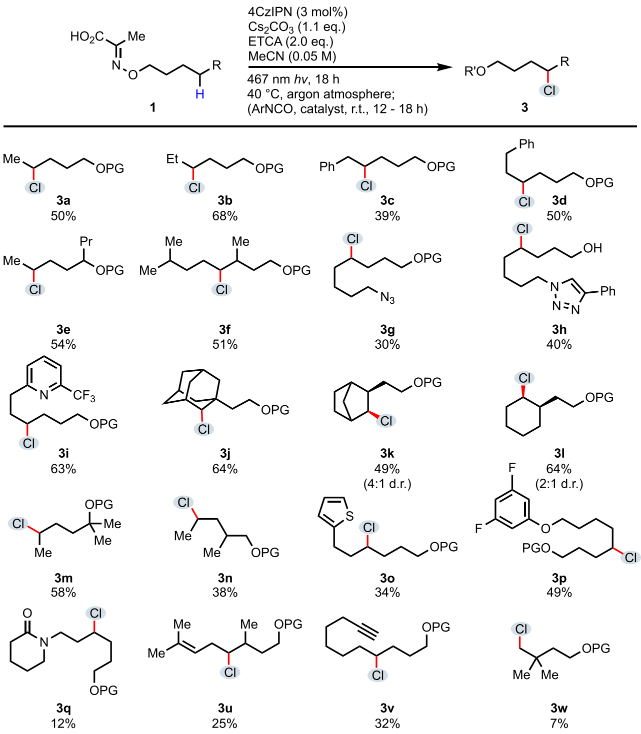
We then proceeded to test the scope of these halogenation reactions with respect to both fluorination (Scheme 2) and chlorination (Scheme 3). In order to reduce the volatility and ease the purification of the products, many of the resulting alcohol products were derivatized to carbamates using 4-nitrophenyl isocyanate. Methylene and methine C−H bonds could be halogenated in moderate to good yields among a range of substrates bearing heterocycles (**2h**, **2i**, **2o**, **2q**, **3h**, **3i**, **3o**, **3q**), azides (**2g**, **3g**), phenolic ethers (**2p**, **3p**) and nearby benzylic C−H bonds (**2c**, **2d**, **3c**, **3d**). The natural product derivatives tetrahydrogeraniol (**2f**, **3f**), norbornane (**2k**, **3k**), and 2-methylvaleric acid (**2n**, **3n**) were all amenable to this halogenation procedure. Because of the propensity of

Scheme 2. Scope of the δ-Fluorination Reaction[a]



[a]All of the reactions were carried out on a 0.2 mmol scale. All of the yields reported are isolated yields. R′ = H or PG. PG = CONH(p-NO_2)C_6H_4. Certain products were isolated in the presence of another regioisomer: **2b** (95:5), **2c** (88:12), **2d** (95:5), **2e** (97:3), **2f** (91:9), **2g** (95:5), **2h** (95:5), **2i** (97:3), **2o** (96:4), **2p** (95:5), **2q** (99:1), and **2s** (97:3). Trace difluorinated product was observed in nearly all cases (see the SI for further details).

Scheme 3. Scope of the δ-Chlorination Reaction[a]



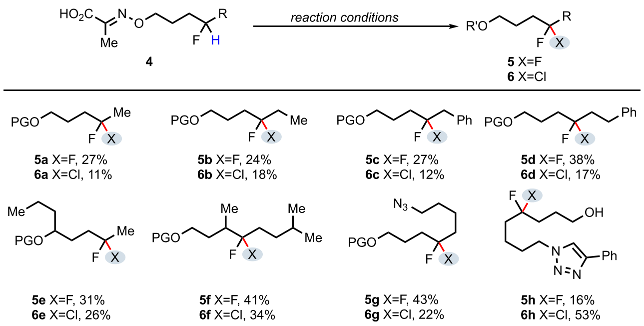
[a]All of the reactions were carried out on a 0.2 mmol scale. All of the yields reported are isolated yields. ETCA = ethyl trichloroacetate. R′ = H or PG. PG = CONH(p-NO_2)C_6H_4. **3d** was isolated in the presence of another regioisomer (94:6). **3q** was isolated in the presence of a product with eliminated chlorine (14 mol%).

Selectfluor to react with unsaturated systems, olefin- (**3u**) and alkyne-containing (**3v**) substrates were successful only for chlorination. In certain substrates, minor amounts of alternate regioisomers were observed, and control experiments (see the SI) indicated that these regioisomers arose mainly from 1,6-HAT as opposed to nondirected C−H abstraction processes.

To test the scalability of our protocol, we attempted the remote fluorination reaction using 1 g of azide-containing starting material **1g**. This reaction proceeded smoothly, providing the fluorinated azido alcohol in 61% isolated yield in only 15 min (see the SI for the procedure). This process is particularly attractive since the oxyimino acid precursor is bench-stable for months and thermally stable up to 100 °C and requires no transition metal catalysts for radical generation. Moreover, this protocol uses Selectfluor, one of the cheapest and most easily handled electrophilic fluorine sources.[36]

Given the power of this methodology for site-selective monohalogenation, we questioned whether reinstallation of the oxyimino acid directing group might enable the remote C−H halogenation reaction to be performed a second time to form valuable dihalogenated methylene groups. Difluoromethylene groups, known for their isosteric and isopolar relationship to oxygen, have played an important role in devising more potent protease inhibitors[37] and nucleoside analogues.[38] Difluoromethylene groups are typically formed by reacting deoxyfluorination reagents such as (diethylamino)sulfur trifluoride (DAST) with preinstalled ketones. In view of the hazards associated with aminosulfuranes and the requirements of cryogenic temperatures and long reaction times, other methods to incorporate difluoromethylene groups are highly sought.[39−41] By the use of our fluorination methodology, it was possible to install difluoromethylene groups at remote positions in moderate yields (Scheme 4).

Scheme 4. Scope of the Dihalogenation Reactions[a]

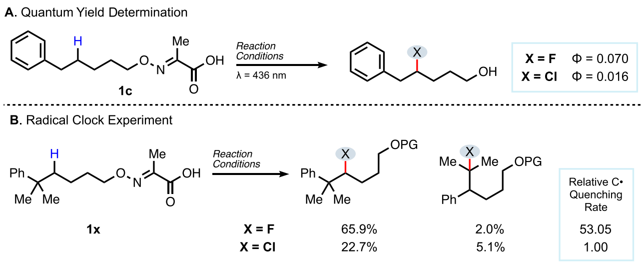


[a]All of the reactions were carried out on at least a 0.1 mmol scale. ETCA = ethyl trichloroacetate. R′ = H or PG. PG = CONH(p-NO_2)C_6H_4. All of the substrates were isolated as inseparable mixtures with their monofluorinated analogues (X = H). Certain products were isolated as regioisomers: **5c** (96:4), **5f** (98:2), and **6c** (99:1). Yields of the stated products were estimated using either ^1H or ^{19}F NMR analysis of the isolated mixtures. Reaction conditions: X = F: 4CzIPN (1 mol %), CsF (2.20 equiv), Cs_2CO_3 (0.5 equiv), Selectfluor (2.0 equiv), MeCN/H_2O (0.05 M, 4:1), 467 nm hν, 10 min, 40 °C, argon atmosphere; (ArNCO, catalyst, r.t., 12−18 h). X = Cl: 4CzIPN (3 mol %), Cs_2CO_3 (1.1 equiv), ETCA (2.0 equiv), MeCN (0.05 M), 467 nm hν, 18 h, 40 °C, argon atmosphere; (ArNCO, catalyst, r.t., 12−18 h).

This dihalogenation strategy could also be extended to generate chlorofluoromethylene groups, albeit in lower yields (Scheme 4). Aliphatic chlorofluoromethylene groups are typically encountered in refrigerants and fire retardants. While methods to introduce the chlorofluoromethylene group into complex molecules as part of a cyclopropane ring through additions of chlorofluorocarbene to olefins are well-established,[42] acyclic chlorofluoromethylene groups are typically synthesized as mixtures of regioisomers using elemental halogens,[43] making their selective introduction to complex molecules extremely difficult. To our knowledge, our strategy is the first method for the regioselective introduction of the chlorofluoromethylene motif into unfunctionalized aliphatic chains.

The stark differences in the times required for the fluorination and chlorination reactions led us to investigate the reaction mechanism. Suspecting that a radical chain might be in operation in the fluorination reaction,[44] we measured the quantum yields of the two reactions (Scheme 5A) as Φ = 0.070 for the C−H fluorination and Φ = 0.016 for the C−H

Scheme 5. Mechanistic Studies



chlorination. Although these results are inconclusive evidence for a radical chain in either reaction, they do show that despite a lower photocatalyst loading, the remote C−H fluorination reaction is photochemically a more efficient process than the C−H chlorination.

We also compared the rates of quenching of the carbon-centered radical from 1,5-HAT through radical clock experiments[45] (Scheme 5B). Using a neophyl-type substrate as the clock,[46] we found that the rate of quenching for the carbon-centered radical was over 53 times higher in the fluorination reaction than in the chlorination reaction. Taken together with the quantum yield measurements, these mechanistic results may help justify the large discrepancy in the times required for these reactions.

In summary, we have developed a new precursor to access alkoxy radicals via photoredox catalysis. By the use of these alkoxy radicals, remote carbon radicals generated by hydrogen atom transfer may be quenched with fluorinating and chlorinating reagents to forge new carbon−halogen bonds. By reinstallation of this directing group, valuable dihalomethylene groups may be generated at remote positions in the molecule. We expect that this new radical precursor will enable a diverse range of new transformations to be developed, both by expansion of the remote C−H transformations reported herein and by taking advantage of the other reaction modes of alkoxy radicals, including β-scission and addition across unsaturated bonds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.9b13171.

> General experimental procedures, optimization studies and control experiments, mechanistic studies, characterization of all key compounds, and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge The Scripps Research Institute and the NIH (National Institute of General Medical Sciences Grant 2R01GM084019) for their financial support. We thank Dr. Jason Chen, Brittany Sanchez, and Emily Sturgell of the TSRI Automated Synthesis Facility for assistance with HRMS measurements and LC work. We thank Prof. Ashok Deniz and Emily Bentley for assistance with photophysical measurements. We thank Dr. Byron Peters (Baran laboratory) for assistance with cyclic voltammetry measurements. We thank Dr. Dee-Hua Huang and Dr. Laura Pasternack for assistance with NMR measurements.

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