$C(sp^3)$–H Fluorination

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The Uranyl Cation as a Visible-Light Photocatalyst for $C(sp^3)$–H Fluorination

*Julian G. West, T. Aaron Bedell, and Erik J. Sorensen**

Dedicated to Professor Martin F. Semmelhack on the occasion of his 75th birthday

Abstract: *The fluorination of unactivated $C(sp^3)$–H bonds remains a desirable and challenging transformation for pharmaceutical, agricultural, and materials scientists. Previous methods for this transformation have used bench-stable fluorine atom sources; however, many still rely on the use of UV-active photocatalysts for the requisite high-energy hydrogen atom abstraction event. Uranyl nitrate hexahydrate is described as a convenient, hydrogen atom abstraction catalyst that can mediate fluorinations of certain alkanes upon activation with visible light.*

Fluorine has gained a privileged position in the fields of medicinal,[1] agricultural,[2] and materials chemistry[3] for the desirable characteristics that it can confer on the constituent matter of each field. Isosteric (but certainly not electronically similar) with hydrogen, the fluorine atom permits modulation of myriad molecular properties, including partitioning behavior, acidity of neighboring groups, and metabolic stability.[4] Fluorine incorporation has traditionally been achieved using prefluorinated building blocks, limiting the possible sources of fluorine to commercially available compounds. Even deoxyfluorination, one of the more robust techniques for the targeted incorporation of fluorine, requires the pre-existence of an oxygen functional group. For this reason, direct, late-stage fluorination of unactivated $C(sp^3)$–H bonds presents an enticing method by which compounds beyond the confines of fine chemicals catalogues might be accessed.[5]

While the fluorination of $C(sp^3)$–H bonds using elemental fluorine has been common since the Second World War,[6] the low selectivity of this transformation, combined with the operationally non-trivial nature of handling elemental fluorine, has fueled the recent interest[5] in selective $C(sp^3)$–H fluorination using safe, bench-stable reagents. Indeed, recent reports from Lectka,[7] Britton,[8] Chen,[9] and Tan[10] suggest that, despite substantial progress in this research field, methods to achieve the transformation are not yet satisfactory. With some exceptions,[11–13] recent strategies for selectively fluorinating $C(sp^3)$–H bonds have largely recruited photoinduced hydrogen atom abstraction (HAT) catalysts (cat.), such as acetophenone, anthraquinone, 1,2,4,5-tetracyanobenzene, and tetra-*n*-butylammonium decatungstate (TBADT, Figure 1), to generate a carbon-centered radical. This radical can react with a fluorine atom source (R_nN-F), typically the electrophilic NF fluorinating reagents *N*-fluorobenzenesulfonimide (NFSI, Figure 1) or Selectfluor (Figure 1), in a mode first recognized by Sammis,[14] to furnish the desired product. These processes are rendered catalytic by the oxidizing nature of the generated radical (denoted R_nN), either aminyl (NFSI) or aminyl radical cation (Selectfluor), which can return the photoreduced HAT catalyst to its initial state. These serviceable methods share one drawback: the need for ultraviolet (UV, or *hν* 200–400 nm) irradiation. While not all UV photoreactions require specialized equipment, many use low efficiency light sources and can induce side reactions. Therefore, it would be desirable to find a photo-HAT catalyst that can be activated by low energy, visible light (*hν* 400–750 nm).[15]

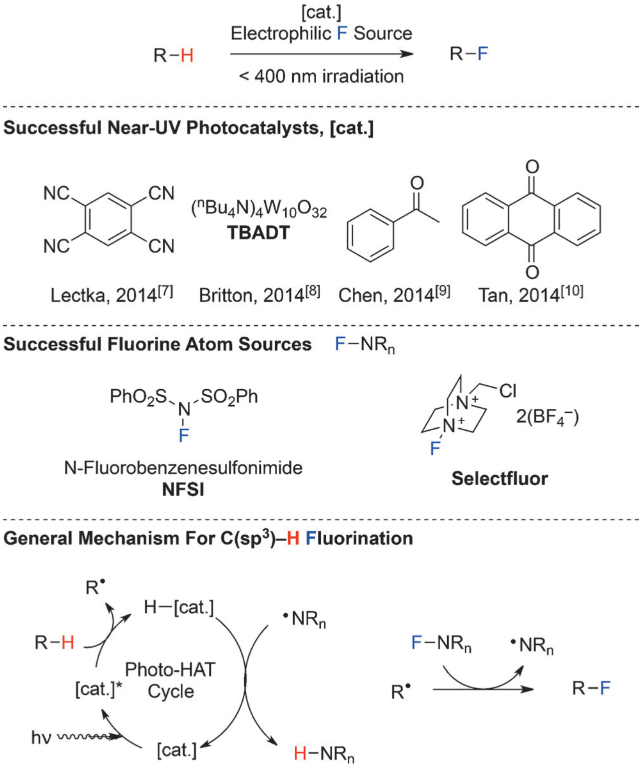

Figure 1. Several near-UV light HAT catalysts and electrophilic fluorine sources used for fluorinations of unactivated C–H bonds and a general mechanism illustrating their function.

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Uranium is an element that has become inextricably linked to the applications of its fissile isotope, ^{235}U, in power generation and nuclear weaponry. Surprisingly, 99.3% of natural uranium is made up of the non-fissile isotope ^{238}U, a species primarily applied as a filler for storage bins near enrichment facilities after removal of ^{235}U (to date, approximately 95% of all depleted uranium produced is stored in this way).[16] The removal of ^{235}U makes handling of depleted uranium no more arduous than the measures required for other heavy metals.[17] Depleted uranium is a substantial untapped resource, as its crustal abundance exceeds that of molybdenum,[18] an element common enough to be used as an enzymatic cofactor. Indeed, despite the glut of depleted uranium, much of its fundamental and structural chemistry has only recently come to light,[19] and its applications in catalysis lag even further behind.[20,21]

One aspect of uranium chemistry that has been well-studied, however, is the photochemistry of the uranyl cation (UO_2^{2+}).[22–24] Studies by multiple groups have revealed that this cation possesses several intriguing characteristics. Notably, a highly oxidizing excited state, $[UO_2]^{2+}*$ (+2.6 V vs. SHE, almost equal to the oxidizing power of elemental fluorine![25]), is accessible under blue light ($h\nu$ 450–495 nm) irradiation. This excited state is sufficiently reactive to abstract hydrogen atoms from unactivated C–H bonds (BDE > 100 kcal mol^{-1}) to generate carbon-centered radicals. Furthermore, pioneering studies by Bakac and co-workers showed that this reactivity could be rendered catalytic for aerobic oxidation of alkanes (Figure 2); with some substrates, the quantum yield approaches unity.[26,27] Despite this promising reactivity and abundance of desirable characteristics, the applications of the uranyl cation in catalysis remain largely underdeveloped.

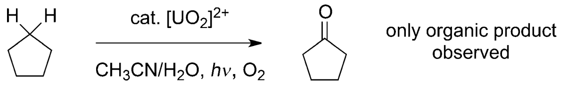
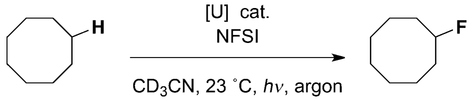


Figure 2. The catalytic aerobic oxidation of alkanes using the uranyl cation has been reported.

Based on this known photochemistry and initial report of catalytic activity, we hypothesized that the uranyl cation would be an ideal photo-HAT catalyst for the fluorination of unactivated C(sp^3)–H bonds via the mechanism outlined in Figure 1. Putting this supposition to the test, we subjected cyclooctane, NFSI, and uranyl acetate dihydrate (1 mol%) to blue LED irradiation to form fluorocyclooctane catalytically, in a modest 8% yield (Entry 1, Table 1). Replacing the uranyl source with uranyl nitrate hexahydrate, led to a greatly improved yield of 52%, corresponding to 52 turnovers (Entry 2, Table 1). Use of a higher intensity blue light source further improved the reaction efficiency, with near quantitative formation of fluorocyclooctane possible after 16 hours of irradiation (>95%/>95 turnovers, Entry 3, Table 1), exceeding the efficiencies of the acetophenone[9] and 1,2,4,5-tetracyanobenzene[7] methods (yields of 82%/16 turnovers and 62%/6.2 turnovers, respectively). Both light and catalyst are required for the reaction, and reduction of the NFSI loading below 1.5 equiv, or the uranyl nitrate loading below 1 mol%, reduced the efficiency of the transformation (Table 1, Entries 4–7). Finally, acetone could be substituted as the reaction solvent with comparable efficiency (Table 1, Entry 8).

Table 1: Optimization of cyclooctane fluorination.



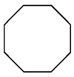
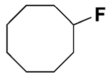
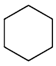
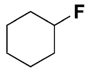
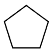
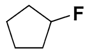
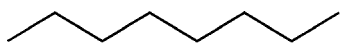
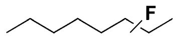
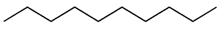
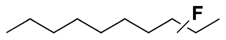
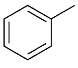
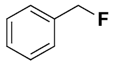
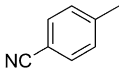
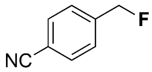
Entry	NFSI [equiv]	Catalyst [mol%]	Light Source[a]	Yield [%][b]
1	1.5	$UO_2(OAc)_2{\cdot}4\,H_2O$ (1)	A	8
2	1.5	$UO_2(NO_3)_2{\cdot}6\,H_2O$ (1)	A	52
3	1.5	$UO_2(NO_3)_2{\cdot}6\,H_2O$ (1)	B	>95
4	1.5	$UO_2(NO_3)_2{\cdot}6\,H_2O$ (1)	none	none
5	1.5	none	B	none
6	1.2	$UO_2(NO_3)_2{\cdot}6\,H_2O$ (1)	B	73
7	1.5	$UO_2(NO_3)_2{\cdot}6\,H_2O$ (0.5)	B	52
8[c]	1.5	$UO_2(NO_3)_2{\cdot}6\,H_2O$ (1)	B	>95

[a] Light source A (high density blue LED strip); light source B (high intensity blue LED lamp); [b] yield determined by comparison of ^{1}H NMR integrals relative to a methyl acetate internal standard; [c] [D$_6$]acetone used as a solvent.

With a rapid, efficient, visible-light-mediated fluorination method in hand, we turned our attention to probing the substrate scope of the reaction. Initial testing found that cyclohexane and cyclopentane C(sp^3)–H fluorination occurred with moderate yields of 42% and 32%, respectively (Table 2, Entries 2 and 3). The cause of this diminished activity is currently unknown. However, a similar reduction in efficiency (though less pronounced compared to cyclooctane) was observed for the fluorination of cyclohexane using both the acetophenone[9] and 1,2,4,5-tetracyanobenzene[7] systems (yields of 59%/12 turnovers and 45%/4.5 turnovers, respec-

Table 2: Fluorination of hydrocarbons.

$$\text{R–H} \xrightarrow[\text{CD}_3\text{CN, 23 °C}, h\nu\text{, argon, 16 h}]{\text{1 mol \% UO}_2(\text{NO}_3)_2{\bullet}6\text{H}_2\text{O} \\ \text{1.5 equiv NFSI}} \text{R–F}$$

Entry	Substrate	Product	Yield [%][a]
1			>95
2			42
3			32
4			55
5			60
6			trace
7			trace

[a] Yield determined by comparison of ^{1}H NMR integrals relative to a methyl acetate internal standard.

tively). n-Alkanes provided a mixture of fluorinated products at non-terminal positions (Table 2, Entries 4 and 5).

A fluorinated motif that occupies a privileged place in the fields of medicinal and agricultural chemistry is the trifluoromethylaryl[28] functional group. To produce this functionality, toluene was subjected to the aforementioned reaction conditions to furnish benzyl fluoride in trace amounts, corresponding to a minimal consumption of starting material and NFSI; 4-cyanotoluene behaved similarly (Table 2, Entries 6 and 7).

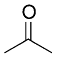
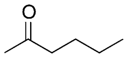
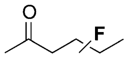
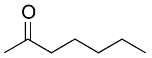
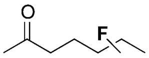
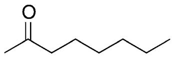
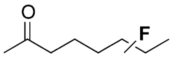
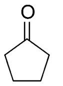
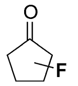
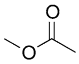
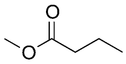
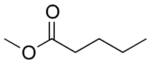
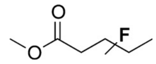
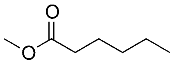
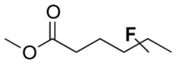
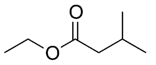
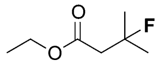
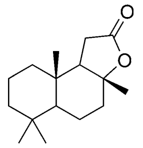
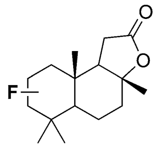
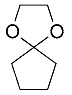
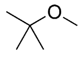
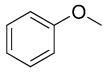
Having achieved some validation of the method on hydrocarbon substrates, our interests turned to the reaction of related oxygenates. Acetone, the simplest aliphatic ketone, displayed no detectable reactivity under our reaction conditions (Table 3, Entry 1). Increasing the chain length of the ketone substrate led to the production of some fluorinated products in trace yields (Table 3, Entries 2–4); cyclopentanone (Table 3, Entry 5) was similarly inert. Residual mass balance corresponded to unreacted starting material in both cases. As with ketones, esters were resistant to fluorination for short chain lengths (Table 3, Entries 6–8), but became suitable substrates as chain length increased, providing distal, internal functionalization (Table 3, Entry 9). Interestingly, ethyl isovalerate (Table 3, Entry 10) performed significantly better than its linear counterpart (Table 3, Entry 8), and the more complex natural product sclareolide performed even better, furnishing 26 % of the combined α- and β-fluorinated products (Table 3, Entry 11). While it appears that proximity to carbonyl functional groups is highly deactivating with respect to the fluorination reaction, the low reactivity of carbonyl-containing substrates cannot be explained by electronic effects alone.

These results from carbonyl-containing substrates are in sharp contrast to those of previously reported photo-HAT fluorination methods, where high reactivity is observed despite sensitivity to electronic effects. For example, sclareolide and acetophenone (80 %/16 turnovers),[9] anthraquinone (77 %/39 turnovers),[10] 1,2,4,5-tetracyanobenzene (61 %/6.1 turnovers),[7] and TBADT (68 %/34 turnovers),[8] all produced mixtures of monofluorinated products in moderate to high yields when compared to the low result observed for the uranium system (26 %/26 turnovers, Table 3, Entry 11). Similarly, acetal and ether functional groups are incompatible with the uranyl system; the dioxolane derived from condensing cyclopentanone with ethylene glycol was even less reactive than the parent ketone (Table 3, Entry 12) and *tert*-butyl methyl ether failed to produce any fluorinated product (Table 3, Entry 13). Taken together, the presence of a Lewis-basic oxygen site on the substrate, even the traditionally weakly coordinating carbonyl group, appears to be deleterious to the reaction.

An initial hypothesis combining these two observations posits that carbonyl groups might be quenching the uranyl excited state via a reversible, inner-sphere electron transfer mechanism. Indeed, it is known that ketones will readily coordinate the labile $[UO_2]^{2+}$ cation, and such intermediates have been observed experimentally.[29] Bakac and coworkers[27] previously observed this non-productive quenching by "exciplex decay" in the aerobic oxidation of toluene, finding that the vast majority of interactions between toluene and the uranyl excited state, $[UO_2]^{2+*}$, led to a return to the ground state with no HAT (Figure 3). We encountered the same phenomenon when attempting to fluorinate toluene and, to an even greater extent, anisole, a substrate that would have been interesting as a model for the production of agrochemically valuable mono-, di-, and tri-fluoromethoxy[30] ethers (Table 3, Entry 14).

Table 3: Fluorination of oxygenated molecules.

$$\text{R–H} \xrightarrow[\text{CD}_3\text{CN, 23 °C, } h\nu\text{, argon, 16 h}]{\text{1 mol \% UO}_2(\text{NO}_3)_2\text{•6H}_2\text{O; 1.5 equiv NFSI}} \text{R–F}$$

Entry	Substrate	Product	Yield [%][a]
1		n/a	0
2			trace
3			trace
4			trace
5			trace
6		n/a	0
7		n/a	0
8			trace
9			13
10			10
11			26[b]
12		n/a	0
13		n/a	0
14		n/a	0

[a] Yield determined by comparison of ^{1}H NMR integrals relative to a methyl acetate internal standard; [b] C2/C3 (1.6:1) fluorination.

Compelling evidence for the exciplex decay of the arene substrates comes from a competitive quenching experiment, wherein an equimolar amount of toluene and cyclooctane were subjected to the fluorination procedure and quantified. The low yields of both products (Figure 4) suggest that this is at least partially responsible for the low observed efficiency. Returning to the question of ketones, an analogous experiment using equimolar cyclopentanone and cyclooctane

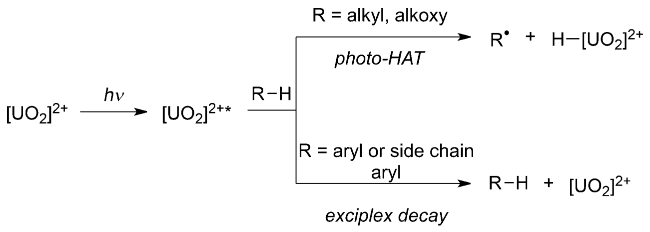


Figure 3. The uranyl excited state $[UO_2]^{2+*}$ reacts with alkanes primarily through hydrogen atom transfer (HAT) and with arenes through unproductive exciplex decay.

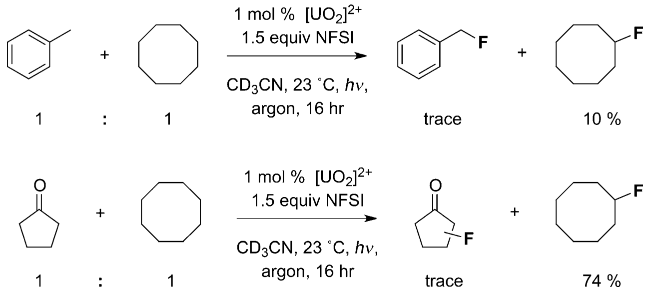


Figure 4. Reactions containing both cyclooctane and toluene (top) or cyclopentanone (bottom) behave differently with respect to reagent conversion. The result with toluene suggests that it is an effective quencher of the uranyl excited state $[UO_2]^{2+*}$.

led to a high yield of fluorocyclooctane (74%, Figure 4) and trace fluorinated cyclopentanone, suggesting that cyclopentanone is at best a weak quencher of the uranyl excited state, $[UO_2]^{2+*}$. If one imagines a slow, but competitive with HAT, intramolecular deactivation pathway for carbonyl compounds, the improved activity of ethyl isovalerate, long chain esters, and sclareolide compared to cyclopentanone could be explained by several factors. These might include, 1) additional activation and thus higher rate of reaction of a methine proton (ethyl isovalerate), 2) a greater number of potential reactive sites (longer chain substrates), and 3) structural rigidity separating the reactive site from a functional group with the potential to quench (sclareolide).

Regardless of cause, the limited substrate scope of the uranyl fluorination, while initially disheartening, offers a number of benefits. Firstly, the (essentially) complete inertness of short-chain ketones and relative unreactivity of other carbonyl compounds contrasts with the TBADT-[8] and acetophenone-mediated[9] reactions, for which they are excellent substrates. In the substrate admixing experiments of Figure 4, the selective activation of cyclooctane (BDE 96 kcal mol^{-1})[32] over toluene (BDE 90 kcal mol^{-1})[33] is interesting and again diverges greatly from arylketone-[9,34] and TBADT-catalyzed[35] fluorination methods, wherein benzylic positions are preferentially activated. This highly discriminating nature of the uranyl catalyst opens the door for selective fluorination of electronically activated C–H bonds in the presence of bonds that would otherwise be a liability under previously reported conditions.

A second upside is the enrichment of the sparse literature describing uranyl photocatalysis. The benchmarking of this promising complex against popular photo-HAT catalysts will allow many valuable contrasts and comparisons to be made in an increasingly well-studied reaction class. The behavior of cyclooctane shows that the efficiency of uranyl photocatalysts can outperform that of traditional near-UV photo-HAT catalysts, while operating under visible light. However, the substrate must be chosen judiciously.

In summary, a new catalytic method for fluorination of certain unactivated C(sp^3)–H bonds was developed. This method uses low-energy visible light to drive homolytic cleavage of strong C–H bonds by an activated uranyl catalyst and capitalizes on the reactivity of a putative organic radical. To the best of our knowledge, this chemistry constitutes the second catalytic transformation based on the HAT reactivity of a photo-activated uranyl catalyst. Our hope is that the research described herein will stimulate future efforts to expand the considerable potential of abundant, yet underutilized uranyl complexes in catalysis.

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