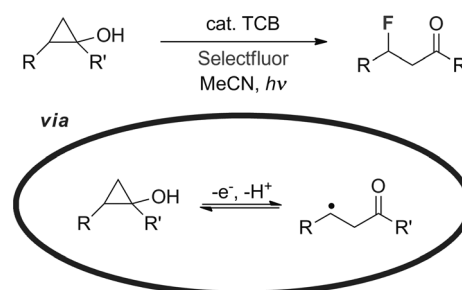


Synthetic Methods

Site-Selective Approach to β -Fluorination:
Photocatalyzed Ring Opening of CyclopropanolsSteven Bloom, Desta Doro Bume, Cody Ross Pitts, and Thomas Lectka^{*,[a]}

Abstract: To expand upon the recent pioneering reports of catalyzed sp^3 C–H fluorination methods, the next rational step is to focus on directing “radical-based fluorination” more effectively. One potential solution entails selective C–C bond activation as a prelude to selective fluorination. Herein, we report the tandem photocatalyzed ring-opening/fluorination reactions of cyclopropanols by 1,2,4,5-tetracyanobenzene (TCB) and Selectfluor to afford a process tantamount to site-selective β -fluorination of carbonyl-containing compounds. This new approach provides a synthetically mild and operationally simple route to otherwise difficult-to-prepare β -fluorinated products in good yields and with good-to-excellent regioselectivity. Remarkably, substrates that contain other usually reactive (e.g., benzylic) sites undergo ring-opening fluorination preferably. The versatility of this method to give cyclic β -fluorides from tertiary cyclopropanols and γ -fluoro alcohols is also highlighted.

cellent mode for directing fluorination, as long as selective formation of the radical cation that prompts C–C bond scission can be achieved. Furthermore, expanding on new advancements in the field, we gathered that photochemistry could play a pivotal role in the development of this tandem ring-opening/fluorination reaction. Accordingly, herein, we report a site-selective photochemical approach to synthesizing a variety of β -fluorinated carbonyl-containing compounds from cyclopropanols (Scheme 1).



Scheme 1. Site-selective β -fluorination of cyclopropanols.

Over the last two years, great strides have been made in the development of direct sp^3 C–H monofluorination methods. However, the methods we^[1] and others^[2] have reported are often limited to the derivatization of highly symmetric compounds, such as cycloalkanes, or those containing one activated site (e.g., benzylic). In substrates that contain many distinct carbon atoms, the problem of “scattershot” fluorination often arises, leading to undesirable mixtures of products. Expanding upon these pioneering initial discoveries, the most logical next step is to focus on directing sp^3 C–F bond formation more effectively, which will allow new and desirable passageways to complex, selectively fluorinated molecules.

Conceptually, two potential routes for a site-selective fluorination event may involve: 1) employing a directing group for C–H activation; or 2) exploring selective C–C activation. In the latter scenario, the use of C–C activation as a means to guide sp^3 fluorination is, to our knowledge, uncharted territory.^[3] To examine this possibility, we envisioned that the one-electron oxidation of highly strained cyclopropanes may serve as an ex-

Our laboratory recently unveiled a photocatalyzed procedure for the monofluorination of aliphatic^[1d] and benzylic^[1g] substrates by using the inexpensive photosensitizer 1,2,4,5-tetracyanobenzene (TCB) along with Selectfluor as a source of atomic fluorine.^[4] This work was accompanied by a number of alternative sp^3 C–H fluorination methods by using photosensitizers, such as fluorenone,^[2d] acetophenone,^[2f] anthraquinone,^[2h] and decatungstate ions.^[2k] Preliminary mechanistic experiments on our benzylic substrates suggest that the reaction proceeds through the formation of a radical-cation intermediate that is rapidly (if not simultaneously) deprotonated to the corresponding benzylic radical (subsequently fluorinated by Selectfluor).^[1g] With this in mind, we deduced that a similar photochemical system may be amendable to substituted cyclopropanol-based starting materials, because: 1) these compounds are known to form radical cations under mild irradiation in the presence of photooxidants due to their high-lying HOMOs^[5] (release of strain energy being the thermodynamic driving force); and 2) the ring opening of radicals generated from cyclopropanols followed by halogen-atom transfer is a well-documented process to access β -halo ketones (or enones).^[6] In the calculated structure of the representative radical cation shown in Figure 1, elongation (to 2.02 Å) of the

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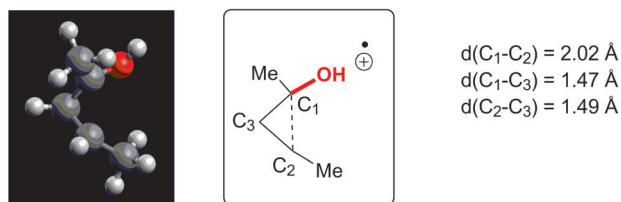


Figure 1. Calculated structure of *trans*-1,2-dimethylcyclopropanol radical cation (ω B97xD/cc-pVTZ, MeCN dielectric).

weakest C–C bond between the C(Me)(OH) and C(H)(Me) fragments is observed. Thus, proton loss should regioselectively afford β -carbonyl radicals that can be subsequently fluorinated. Additionally, cyclopropanols represent attractive substrates for fluorination, because they are readily accessible (e.g., through the Simmons–Smith^[7] and Kulinkovich^[8] reactions) and are suitably reactive, a feature borne of their high-strain energy.

Beyond proof-of-concept, note that the target β -fluorinated carbonyl-containing compounds are synthetically and medically useful. For example, the incorporation of a single fluorine atom at the β -position has been shown to influence the conformational integrity of cyclic amines and amides,^[9] prevent mitochondrial β -oxidation of fatty acids,^[10] and serve as an adequate positron emission tomography (PET) probe for elucidating a number of biosynthetic and metabolic pathways.^[11] Consequently, a number of methods have emerged pertaining to the targeted synthesis of β -fluorinated carbonyl compounds.^[1c,f,g,12,13] It stands to reason that the development of an alternative, photocatalytic route to β -fluorides from cyclopropanols would be highly desirable, providing a much needed tool in the armamentarium of the medicinal chemist.

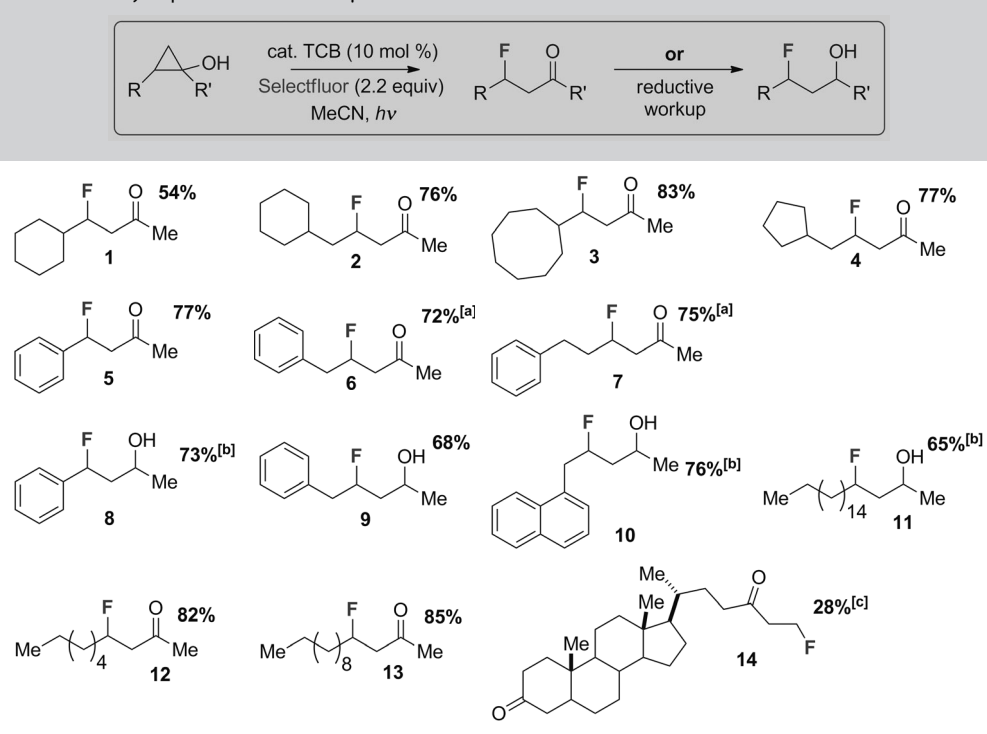
To begin our studies, we selected 2-cyclohexyl-1-methylcyclopropanol for screening purposes. Gratifyingly, UV irradiation ($\lambda = 302$ nm) with catalytic TCB (10 mol%) and Selectfluor (2.2 equiv) at room temperature gave the β -fluoride **1**, derived from preferential scission of the most substituted C–C bond, in 54% yield. Note that in the absence of TCB, no fluorinated products were observed. In addition, heating of 2-cyclohexyl-1-methylcyclopropanol and Selectfluor in MeCN gave an approximately 1:1 mixture of α - and

β -fluorinated ketones and other fluorinated products; evidently, selective β -fluorination is only achievable under photocatalytic conditions. Moreover, other N–F reagents were also examined and found to give lower yields. With these findings in mind, we decided to examine a variety of cyclopropanols derived from vinyl and allyl cycloalkanes, as well as aryl compounds. In each instance, β -fluorinated products were obtained in good to moderate yields and with excellent regioselectivity (Table 1).

Remarkably, the reaction is highly selective toward C–C bond cleavage/fluorination over direct sp^3 C–H fluorination, despite the previous application of a similar system to aliphatic fluorination.^[1d] Compounds **1–4** contain multiple potential fluorination sites on the cyclopentane, cyclohexane, and cyclooctane rings, but only trace ring fluorination products were observed in the ^{19}F NMR spectra of the crude products, avoiding the aforementioned issue of scattershot fluorination. Additionally, the selective formation of β -fluorinated compounds **5–7** reflects the tendency of cyclopropanols to direct the fluorination event. Benzylic starting compounds of **6** and **7** offer a much tougher test than **5**, but even in the presence of a more activated benzylic site, C–C bond cleavage is still favored, providing β -fluorinated products in upwards of 72% yield, although trace amounts of putative benzylic products are observed in some cases.

Upon isolation, we observed a propensity for some of the molecules to undergo elimination to form enones when chro-

Table 1. Survey of β -fluoroketones and γ -fluoroalcohols.



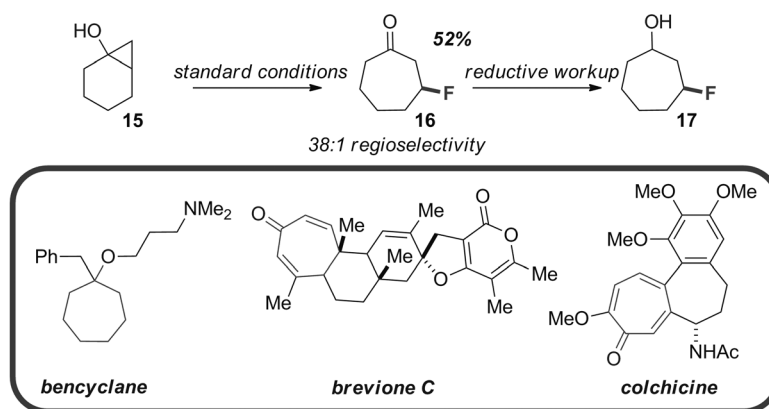
All reactions were performed under an inert atmosphere of N_2 and irradiated with either a UV pen lamp ($\lambda = 302$ nm) or Rayonet reactor ($\lambda = 300$ nm) for 16 h. [a] Isolated as the major fluorinated product with minor fluorinated isomers. [b] Crude reaction mixture redissolved in THF and stirred with LiAlH_4 (5.0 equiv) for 2 min. Isolated as a mixture of diastereomers. [c] Substrate for which xanthone was used as the photocatalyst.

matographed on silica or alumina under neutral, acidic, or basic conditions. It is important to note that elimination can be minimized by using flash chromatography on acidic florisil, which allowed us to isolate most β -fluorinated products with typically $\leq 5\%$ eliminated by-products. In particularly sensitive cases, we found that a reductive workup by using LiAlH_4 allows effective isolation of the corresponding γ -fluoro alcohols after purification by chromatography on silica gel in approximately 1:1 diastereomeric ratio (8–11).

To probe the selectivity of the reaction in situations when indiscrimination fluorination could be especially problematic, we turned our attention to cyclopropanols possessing linear aliphatic side chains. These compounds could conceivably serve as precursors to β -fluorinated fatty acids, proteo-counterparts of which are frequently metabolized by oxidative cleavage of a $\beta\text{-C-H}$ bond.^[14] The selective inclusion of a single fluorine atom at the β -position could therefore prove particularly useful in deterring this pathway.^[15] Furthermore, monofluorinated lipids have found considerable use as probes for studying the interaction between drugs or peptides and lipid membranes.^[16] Toward this effort, we found that 10-, 14-, and 20-carbon β -fluorinated ketones 11–13 could be prepared from the respective cyclopropanols. Polyfluorination and direct aliphatic fluorination were not competitive with β -fluorination, because compounds 11–13 were isolated in 65–85% yield.

In another example, ring opening/fluorination of a non-natural steroid, a methyl-lithocholate derivative,^[17] was found to give the primary fluoride 14 in 28% yield. As was expected, yields for primary β -fluorides were often lower than secondary, a possible result of the diminished stability of primary radicals compared to secondary, but they are still accessible by this method. In an effort to improve these results, we found that replacement of TCB by xanthone as the active photocatalyst provided moderate increases in yields. Terminal alkyl fluorides have been shown to be effective reagents for inexpensive nickel or copper-catalyzed cross-coupling reactions,^[18] but direct syntheses through sp^3 C–C or C–H activation are extremely limited due to preparative difficulty.

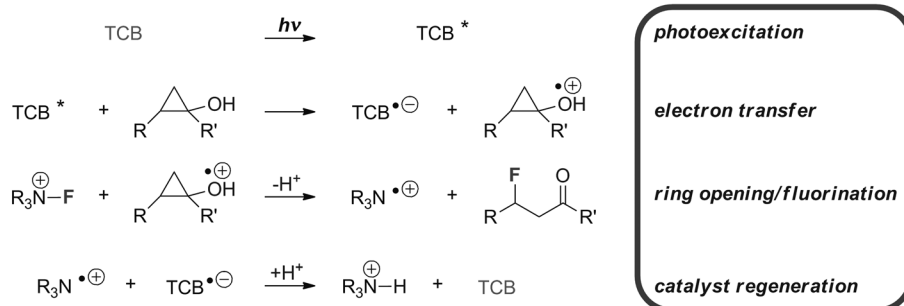
At this point, we considered alternative applications for this method. We explored the use of a tertiary cyclopropanol that could undergo oxidative ring opening/fluorination to give



Scheme 2. Tandem ring expansion/ β -fluorination to access cycloheptanone or cycloheptanol core.

a ring-expanded β -fluoride. For a representative example, we selected cyclopropanol 15, because tandem ring expansion/fluorination should give β -fluorocycloheptanone. Cycloheptanone cores are present in pharmaceuticals, such as bencyclane, a spasmolytic agent and vasodilator, as well as a vital constituent in many fragrances and polymers (Scheme 2).^[19] In this instance, photochemical fluorination proceeded smoothly to give β -fluorocycloheptanone 16 in 52% yield, as was determined by ^{19}F NMR analysis (regioselectivity 38:1). This product was isolated more effectively after purification by chromatography on silica gel as the corresponding γ -fluoro alcohol.

Finally, a general mechanistic proposal for the reaction is shown in Scheme 3. Photoexcitation of TCB is known to yield



Scheme 3. Proposed mechanism for photocatalyzed site-selective β -fluorination.

a powerful oxidant that, in this instance, putatively abstracts an electron from the substrate.^[20] The resultant cyclopropanol radical cation prompts C–C bond elongation while relieving ring strain (Figure 1); this is accompanied by proton loss to selectively afford a β -carbonyl radical. As was expected, Selectfluor can then act as an atomic source of fluorine to directly fluorinate the radical.^[1e,4] Lastly, the Selectfluor radical cation retrieves the electron from the TCB radical anion, as well as the excess proton from the reaction medium, thus generating an ammonium salt by-product and regenerating the TCB catalyst.

In conclusion, a photocatalyzed protocol for the selective ring-opening/ β -fluorination reactions of cyclopropanols is reported. This system is synthetically mild, operationally simple, and can be employed to afford a number of electronically and sterically diverse β -fluorinated carbonyl-containing compounds and γ -fluorinated alcohols. Furthermore, various fluorinated products with medicinal and agrochemical values can be prepared by employing this method. Continued work will seek to elucidate the precise mechanism of the photochemical fluorination system along with the application of this method to the synthesis of complex fluorinated molecules.

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Keywords: C–C activation • cyclopropanols • fluorination • photochemistry • radical ions

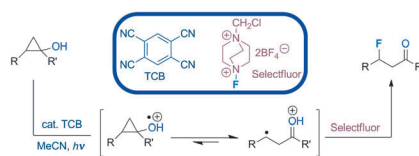
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The tandem photocatalyzed ring-opening/fluorination reactions of cyclopropanols by 1,2,4,5-tetracyanobenzene (TCB) and Selectfluor to afford a process tantamount to site-selective β -fluorination of carbonyl-containing compounds are reported (see scheme).



Synthetic Methods

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T. Lectka*

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Site-Selective Approach to β -
Fluorination: Photocatalyzed Ring
Opening of Cyclopropanols

