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A photocatalyzed aliphatic fluorination†

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We disclose a new approach to the catalysis of alkane fluorination employing ultraviolet light and a photosensitizer, 1,2,4,5-tetracyanobenzene (TCB). The process is efficient, mild, and operationally straightforward. We demonstrate reaction utility on a variety of substrates, from simple hydrocarbons to complex natural products. In a showcase example, we establish that the well-known photochemical rearrangement of α-santonin can be supplanted by a highly selective catalyzed fluorination.

Introduction

The value of organofluorine compounds to all branches of chemistry has increased exponentially over the past decade, from pharmaceutical science[1] to materials development[2] and synthesis.[3,4] Attending this explosive increase in scientific importance has been the quest to develop mild methods of fluorination, which are usually subdivided into two main areas wherein the fluorine atom acts as either an electrophile or a nucleophile.[5] Electrophilic fluorination, especially that involving C–H bond functionalization, has been historically characterized by the use of potentially dangerous, high energy reagents such as F_2 gas,[6] the explosive solid $CsSO_4F$,[7] and CoF_3,[8] which acts at high temperatures to afford polyfluorinated products. Paradoxically, although C–F bonds are strong (>100 kcal mol^{-1}), energetic reagents have been historically needed to form them. Recently, an active and timely area of interest has been the development of mild methods for aliphatic fluorination. These have unsurprisingly involved catalysis: the work of Groves, using Mn(porphyrin) complexes,[9] and our work using copper catalysis.[10] We thought it would be of interest to devise a simple, complementary procedure that obviated the use of transition metals yet could produce products in high yields and selectivities. In this paper, we report a new approach to the catalysis of alkane fluorination employing ultraviolet light and 1,2,4,5-tetracyanobenzene (TCB) as a photosensitizer. This system overcomes the high oxidation potential of alkanes by way of a photoinduced electron transfer providing direct access to putative alkyl radicals that may be readily fluorinated in the presence of an electrophilic fluorinating reagent, Selectfluor.

Although highly desirable, selective methods for the direct functionalization of simple hydrocarbons remain limited, often requiring the use of strong and/or poorly selective reagents (*e.g.* transition metal oxo complexes, *N*-oxo radicals, or organic peroxides).[11] Recently, it has been shown that the excited states of certain organic molecules can act as sufficient one-electron oxidants for the selective cleavage of (sp^3C)–H bonds.[12] For example, TCB, when sensitized by ultraviolet light (λ_{max} = 266 nm), is known to remove an electron from alkanes.[13] The resultant radical cations are very acidic and ephemeral species, presumably rapidly yielding alkyl radicals in turn. As such, adamantane radical cation affords the corresponding 1-yl, which then alkylates TCB itself.[11,12] It occurred to us that if an electrophilic fluorinating agent were present, fluorination could occur preferentially if the reagent were more active than the rebounding TCB. Sammis *et al.*, in pioneering work, have shown that alkyl radicals can in fact be efficiently fluorinated by electrophilic reagents, especially *N*-fluoro-*N*,*N*-bis(phenyl-sulfonimide).[14] More recently, fluorination of alkyl radicals by Selectfluor has been demonstrated by Li *et al.*,[15] and Inoue *et al.*[16] under catalytic conditions. It was our idea to use TCB and UV light in conjunction with Selectfluor, an easy-to-handle, commercially available source of electrophilic fluorine. Ideally, radical cation formation is followed by fast loss of a proton to solvent (acetonitrile) producing the radical, which can then be readily fluorinated (Fig. 1).

Our reaction system consists of a simple UV lamp, a water bath, and a culture tube containing the reagents under an inert atmosphere of N_2. The first substrate that we examined for screening purposes was cyclododecane, as all C–H bonds are equivalent and the product monofluoride can be easily isolated and characterized. After Selectfluor, substrate, MeCN, and TCB (10 mol%) are added to the flask, UV irradiation is applied for 16 h. At the onset, cyclododecane proved to be a propitious

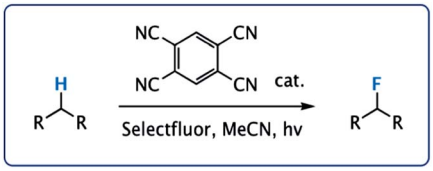

Fig. 1 Photocatalyzed aliphatic fluorination.

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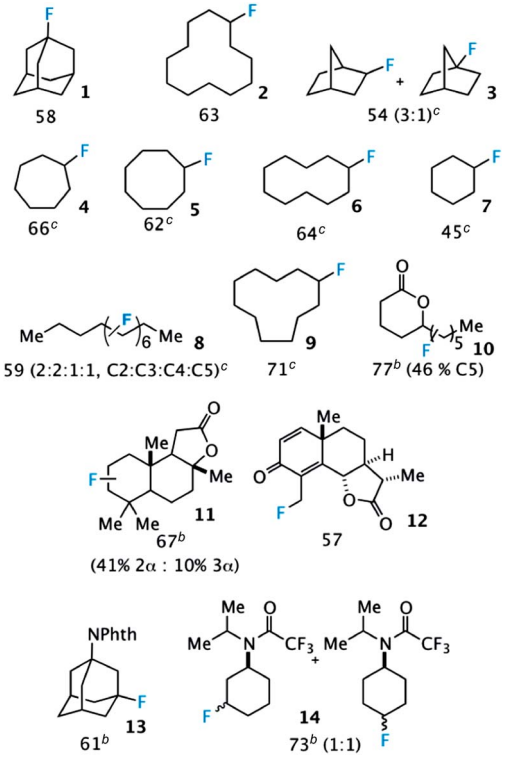
choice for screening; it monofluorinates preferentially, affording fluorocyclododecane in 63% yield. To our gratification, only trace amounts (at most) of the arylated alkane were identified. Although reactions were performed over 16 h, the majority of aliphatic substrates were completely converted within the first 6 h by TLC and/or monitoring by ^{19}F NMR.

A working hypothesis for the mechanism of the reaction is shown in Fig. 2. Given precedent,[11,12] we postulate TCB sensitization, radical cation formation, loss of a proton to solvent, fluorination of the resulting radical, back-electron transfer from TCB to the ammonium radical cation, and proton transfer from solvent. TCB is thus regenerated, and can act again.

At this point, we decided to screen a host of cyclic and linear alkanes under our reaction conditions. Much to our liking, monofluorinated products were obtained in moderate to good yields and in fair selectivities (Table 1). In many instances, fluorination occurs at the carbon in accordance with relative radical stability. However, this is not always the case; whereas adamantane reacts under our photolytic conditions to afford 1-fluoroadamantane, norbornane yields the methylene monofluoride predominantly. Moreover, *n*-dodecane fluorinates considerably at C2 through C5, while minimally at C1 or C6. It should be noted that for some substrates, particularly small cycloalkanes with a fair degree of strain energy, nonselective fluorination in the absence of photocatalyst was observed (<8%), a result consistent with Selectfluor's ability to act as a sufficient oxidant combined with the increased reactivity of strained alkanes. In such cases, we found that use of *N*-fluoro-*N*,*N*-bis(phenylsulfonimide) or *N*-fluoropyridinium tetrafluoroborate as sources of electrophilic fluorine eliminated side reactions completely, albeit with lower yields of fluorinated product and longer reaction times. This result is in direct contrast to our previously reported copper-catalyzed system in which the use of other *N*-F reagents proved ineffective, yielding no fluorinated products.[7]

In light of our success with simple alkanes, we next turned our attention to more complex substrates. Of importance: (1) sclareolide (entry **11**) demonstrated stereoselective α-fluorination at C2 and C3 of the A ring in a roughly 4 : 1 ratio respectively, a similar finding to Groves *et al.* using a Mn(porphyrin) catalyst, iodosobenzene as an oxidant and silver fluoride;[8] (2) aliphatic amides **13** and **14** were fluorinated under our reaction conditions; (3) competitive C–C bond fragmentation and/or secondary photochemical reactions of major fluorinated products, especially open-chained alkanes, **8** and **10**, was virtually undetectable; (4) difluorination and rebound arylation from the photocatalyst is negligible.

Table 1 Survey of fluorinated alkanes[a]



[a] All reactions were performed under an inert atmosphere of N_2 and irradiated at 302 nm for 16 h. [b] Isolated as the major fluorinated product with minor fluorinated isomers. [c] Yield based on ^{19}F NMR using 3-chlorobenzotrifluoride as an internal standard.

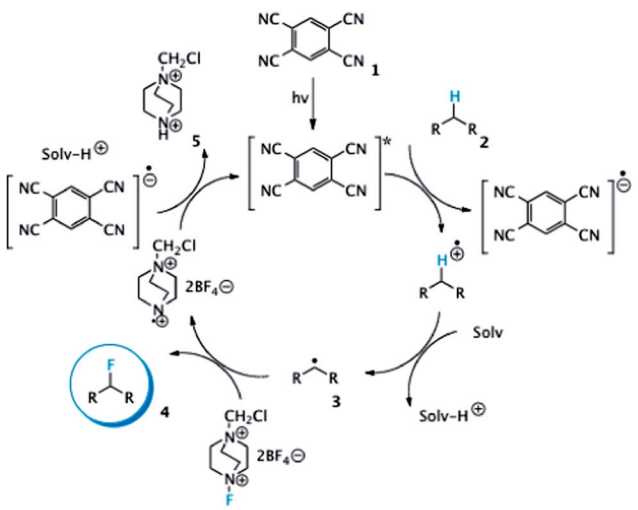


Fig. 2 Working hypothesis for reaction mechanism.

Having demonstrated the reliability of our system for a host of simple to moderately complex alkanes, we thought it would be of interest to perform some initial mechanistic experiments, perhaps enabling us to improve our reaction further. In particular, we questioned the extent to which TCB was able to selectively absorb light in the presence of a competitor – namely a *photoactive* substrate and our fluorinating reagent. To examine this question, we envisioned the use of a well-known natural product that undergoes photochemical rearrangement upon irradiation (302 nm). The efficiency of our photocatalyst could thus be related to the extent of rearranged product in our reaction mixture. Toward this effort, the photoactive sesquiterpene lactone, α-santonin, was selected as a prototypical substrate. Under irradiative conditions, α-santonin undergoes a well-documented structural rearrangement initiated by

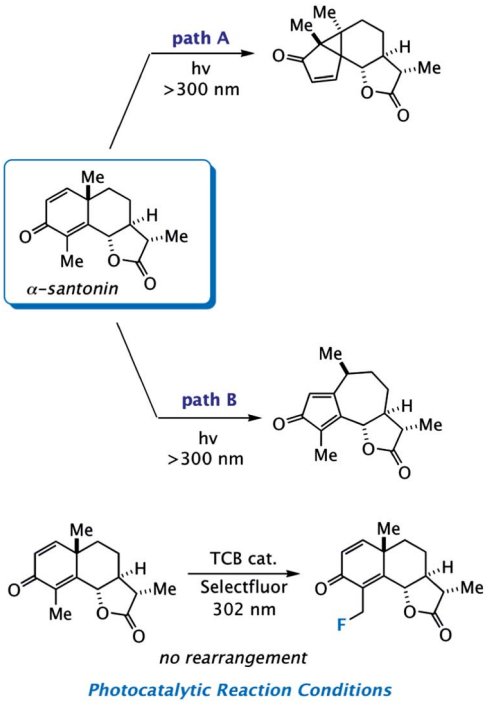


Fig. 3 Photoinduced reactions of α-santonin.

cleavage of bond C4–C5 (path A) or C3–C4 (path B, Fig. 3);[17] as well, the resulting products should be suitable substrates for fluorination. However, under our conditions, fluorination of the α-methyl group was observed *exclusively*. Despite the classical propensity for rearrangement of dieneones, minimal to no structural reorganization of α-santonin was evident even after continued irradiation of the product allyl fluoride for an additional 16 h. It may be postulated that the rearrangement of α-santonin in MeCN is slower than that for the rate of fluorination, such that the addition of fluorine prevents isomerization.

Alternatively, selective sensitization of TCB or Selectfluor may inhibit sufficient irradiation of α-santonin required for rearrangement. In an attempt to answer this question, a series of control experiments was performed. In the absence of both photosensitizer and Selectfluor, rearrangement to the cyclopropyl ketone, lumisantonin (path A), occurs in high conversion. Conversely, in the absence of only the sensitizer, trace amounts of fluorinated product are observed along with a significant quantity of rearranged product. Finally, when α-santonin is irradiated at 302 nm with only sensitizer present, isomerization is again minimal, indicating that TCB *inhibits* isomerization. We therefore conclude that preferential TCB sensitization followed by fluorination is the most likely pathway. Once fluorinated, rearrangement of the product does not occur to any significant extent. To our knowledge, this finding not only demonstrates the first preparative method for allyl fluorosantonins, but may be of considerable interest to continued efforts in elucidating their rich photochemistry (Fig. 4).

Finally, we decided to undertake a preliminary investigation regarding the involvement of radicals in the reaction. In doing so, we selected the α,β-unsaturated aryl ester 16 as it is a proven probe for benzylic radical cyclizations.[18] It is anticipated that formation of the corresponding benzylic radical could lead to the standard fluorinated product 17 and/or the more diagnostic product 18 through a cyclization reaction. Experimentally, irradiation of 16, TCB, and Selectfluor over 16 h afforded a crude mixture of both products whose identity was determined by comparison to known literature values.[19] Additionally, the reaction was conducted in the presence of a known radical inhibitor, TEMPO. Although no trapped products could be isolated, the incorporation of TEMPO at any point during the reaction was found to inhibit the reaction, yielding little to no fluorinated products. The observed decrease in yield is also indicative of the participation of radicals, although further studies are needed to elucidate their exact role.

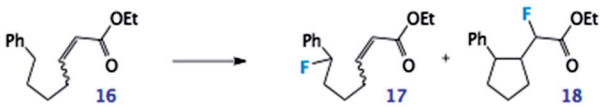


Fig. 4 Radical clock analysis of α,β-unsaturated aryl ester.

Conclusion

Continued efforts to discern the precise mechanism of this new reaction will be made in addition to the search for new applications of our system to chemical synthesis, C–H activation and photocatalysis for the construction of complex fluorinated molecules.

Experimental section

Representative procedure for the syntheses of fluorinated alkanes: an 13 × 100 mm glass culture tube equipped with a stir bar and septum was placed under an atmosphere of N_2. Cyclododecane (42.0 mg, 0.25 mmol, 1.0 equiv.), Selectfluor (195 mg, 0.55 mmol, 2.2 equiv.) and 1,2,4,5-tetracyanobenzene (4.45 mg, 0.025 mmol, 0.1 equiv.), were then added, followed by MeCN (3.0 mL). The reaction mixture was then placed in a water bath and irradiated using a UV Pen Lamp at 302 nm for 16 h. The reaction progress was monitored by TLC using an eluent of hexanes. Final yields were determined either by ^{19}F NMR spectroscopy using 3-chlorobenzotrifluoride as an internal standard or column chromatography on silica (either method was in good agreement).

Acknowledgements

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