Organic LETTERS

Letter

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Photocatalyzed Benzylic Fluorination: Shedding "Light" on the Involvement of Electron Transfer

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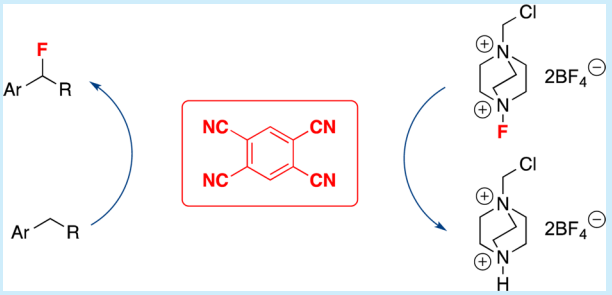
Supporting Information

ABSTRACT: The photocatalyzed oxidation of benzylic compounds by 1,2,4,5-tetracyanobenzene (TCB) in the presence of Selectfluor provides a synthetically efficient route to electron deficient, less substituted, and otherwise inaccessible benzylic fluorides. The virtue of this system is multifold: it is metal-free and mild, and the reagents are inexpensive. Mechanistically, the data suggest the intimate formation of intermediate radical cations in the key radical forming step, as opposed to a concerted hydrogen atom transfer process.



As any conscientious student of organic chemistry knows, benzylic halogenations represent historically important chemical reactions.[1] Free radicals are often of paramount importance in benzylic halogenations and, as such, have been harnessed to give rise to chlorinations and brominations.[2] Benzylic fluorinations, especially using a hazardous reagent such as fluorine gas, are much more difficult;[3] therefore, straightforward and mild protocols for benzylic fluorination are desirable. An early example stems from the work of Sanford, who used chelating substrates in Pd(II) catalysis.[4] This discovery was followed by our work employing either a copper(I) based system[5] or $Fe(acac)_2$ as a catalyst,[6] followed by Groves's results with Mn-salen catalysts[7] and Inoue's work on benzylic substitution through nitroxyl radical catalysis.[8] All of these protocols save one involve metal catalysis. Very recently, we reported a new method for aliphatic fluorination using the photocatalyst 1,2,4,5-tetracyanobenzene (TCB), Selectfluor, and MeCN as solvent.[9] This work was accompanied by a number of alternative sp^3 C−H fluorination methods by others using a host of photosensitizers including decatungstate ions,[10] anthraquinone,[11] and fluorenone.[12]

At least in some cases, it is widely held that photoexcited 1,2,4,5-tetracyanobenzene may operate by the abstraction of *electrons* from the substrate rather than hydrogen atom transfer (HAT), thereby forming discrete radical cations (Figure 1).[13] We envisioned such a system could prove complementary to catalysts believed to act through a HAT mechanism and useful for the fluorination of less reactive primary and secondary benzylic substrates.[14] Although TCB requires excitation at wavelengths in the same spectral window as many common organics (<320 nm), our laboratory has shown it to absorb light selectively in the presence of the photolabile anthelminthic, α-santonin, leading to a single fluorinated product instead of the substrate being compelled to undergo other precedented photochemical reactions.[9] We now report our studies on a

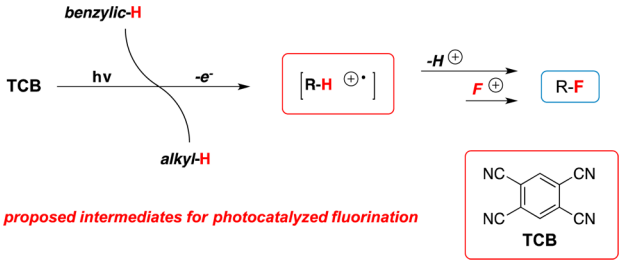


Figure 1. Photocatalysts for sp^3 C−H fluorination.

photocatalyzed benzylic fluorination using commercially available photosensitizer TCB and the electrophilic fluorinating agent Selectfluor. In comparison to complementary methods, this system offers shortened reaction times and an expanded substrate scope to include electron deficient, 1°, 2°, and previously unreactive benzylic substrates through a putative electron transfer process to form intermediate radical cations.

We surveyed a number of benzylic compounds for reactivity using MeCN solvent, excess Selectfluor, and 10 mol % TCB, under photolysis with a pen lamp (λ_{max} = 302 nm, Figure 2). Examination of the products depicted in Figure 2 highlights the selectivity for monofluorination at sterically accessible benzylic positions (methine or methylene) even in the presence of remote electron-withdrawing groups such as carbonyls, α,β-unsaturated ketones, or other functional groups that labilize adjacent protons. For simple alkylbenzenes, the relative reactivity of C_α−H bonds for methyl, ethyl, and isopropyl groups was determined. Interestingly, the rate of fluorination appears to *decrease* in the order 2° > 1° ≥ 3°, a result generally thought to be inconsistent with a free radical chain reaction (^{i}Pr

Received: October 22, 2014
Published: December 10, 2014

   dx.doi.org/10.1021/ol503094m | *Org. Lett.* 2014, 16, 6338−6341

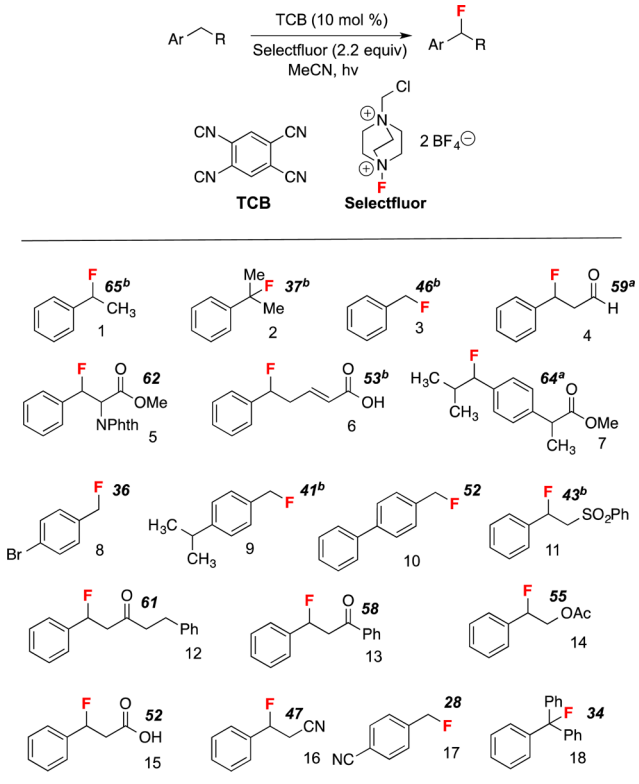


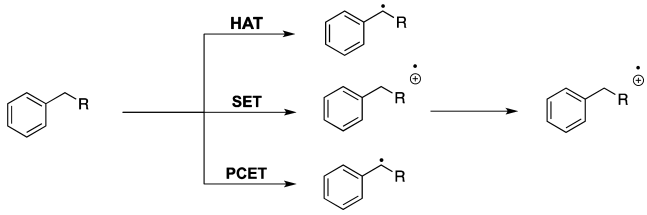
Figure 2. Survey of benzylic fluorinated products. All reactions were performed under an inert atmosphere of N_2 and irradiated with a UV pen lamp (302 nm) for 24 h. [a] Isolated as the major fluorinated product with minor fluorinated isomers. [b] Yield determined by ^{19}F NMR using 3-chlorobenzotrifluoride as an internal standard.

> Et > Me).[15] Similarly, in the case of cymene, regioselective fluorination of the methyl group occurs despite the presence of a suitably reactive isopropyl substituent. Assuming formation of a radical cation, deprotonation of the methyl group is preferred due to the favorable π-C−H overlap that could be precluded in the isopropyl group for steric reasons.[16] Of further significance, we found that an unprotected benzylic aldehyde could be fluorinated without risk of acid fluoride formation, a common problem encountered with aldehydes in other benzylic fluorination protocols. Finally, electron-deficient aromatics demonstrated some reactivity although these substrates have proven challenging to functionalize by alternative methods.

Considering the value of fluorinated amino acids to drug discovery and their potential utility in PET imaging, we next examined the fluorination of a phthalimide derived from *rac*-phenylalanine. Gratifyingly, fluorination proceeded smoothly to afford the fluorinated amino acid methyl ester **5** in 62% yield (1:1 diastereomeric mixture). It is also important to note that no decarboxylation was detected in carboxylic acid containing substrates, in contrast to precedent.[17] We also found that direct fluorination of the protected nonsteroidal anti-inflammatory (NSAID) ibuprofen methyl ester and pharmacophore dihydrochalcone could be achieved in 64% (compound **7**) and 58% (compound **13**) yields, respectively.

At this point, we undertook some preliminary mechanistic experiments. Typically, photocatalyzed reactions proceed through one of a number of possible modes of action, including hydrogen atom transfer (HAT), electron transfer (ET), or a variety thereof termed proton-coupled electron transfer (PCET) (Scheme 1).[18] In the traditional HAT

Scheme 1. Generation of Radical Intermediates during Fluorination



mechanism, homolytic hydrogen abstraction from a C−H bond results in formation of a nucleophilic carbon-centered radical that can react with various electrophiles. In an ET mechanism, either an oxidative or reductive activation is involved through formation of an electron donor−electron acceptor complex, permitting passage of electrons from one species of the exciplex to the other; the result is thus the formation of radical cations and anions.[19] In the case of PCET, transfer of an electron occurs with simultaneous loss of a proton to or from the substrate. This pathway is often encountered in biological and electrochemical systems displaying high redox activity and complexity.[20]

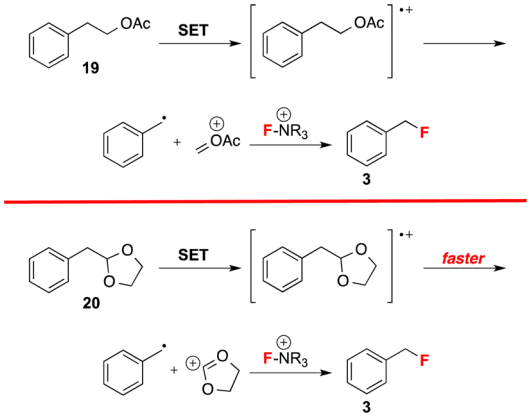
To distinguish between these mechanisms, several parameters must be explored in more detail. Early work by Baciocchi[21] on the mechanism of side-chain oxidation of alkylbenzenes established that HAT and ET mechanisms exhibit distinctive selectivity patterns, thus representing a suitable probe for discerning between these two pathways. Baciocchi found that, in HAT mechanisms, the reactivity order ^{i}Pr > Et > Me is qualitatively observed. This finding may be explained by the fact that, in the HAT transition state, considerable breakage of the C−H bond occurs, and the C−H bond dissociation energy (BDE) increases in the progression 3° C−H < 2° C−H < 1° C−H. However, in the case of ET mechanisms, Baciocchi noted that the ^{i}Pr group is *always* less reactive than the Et group, and in a few cases even less reactive than the Me group. This finding is rationalized given that, in an ET mechanism, selectivity is determined in the radical cation deprotonation step, that, being irreversible, is also the step controlling the product distribution (in the manner of cymene). Moreover, cleavage of the C−H bond must be accompanied by an extensive electronic reorganization during which electrons from the benzylic C−H bond are transferred in part to the aromatic π-system, and it has been shown to possess a strong stereoelectronic component.[21] Analysis of the products in Figure 2, namely compounds **1**, **2**, and **3**, suggests an ET mechanism for our reaction based on product yields alone; in fact, a competition experiment between these substrates revealed fluorination of ethylbenzene occurred *exclusively*. This finding is in direct contrast to our copper(I) catalyzed system, which has been recently shown to operate through a HAT mechanism.[22] In the copper system, competitive fluorination between toluene, ethylbenzene, and cumene is observed in a ratio of 1:6.4:3.8, the mild preference for ethylbenzene over cumene being attributed to a simple steric repulsion between proton abstractor and substrate. The difference in selectivities between these systems points to the possible influence of an alternative mechanism, most likely, an electron transfer process. This possibility is further augmented by an examination of the reactivity of a series of *p*-substituted toluene derivatives. Considering the rates of fluorination for *p*-bromotoluene, toluene, and *p*-cyanotoluene, *p*-cyanotoluene

dx.doi.org/10.1021/ol503094m | *Org. Lett.* 2014, 16, 6338−6341

was found to react the slowest, while toluene reacted the fastest. This order correlates nicely with relative radical cation stabilities.

To probe the involvement of radical cations in our reaction, we envisaged the use of a compound that could render two distinct products depending on the initial intermediate formed, a benzylic radical or radical cation. We chose two candidates: 1-phenylethyl acetate **19** and 2-benzyl-1,3-dioxolane **20**, both of which are expected to form radical cation intermediates that can fragment into a benzyl radical and a stabilized cation. For example, calculation of $\mathbf{19}^{\bullet+}$ at PBEPBE/cc-pVTZ shows a slightly elongated Ar**C**−CO β-bond (1.525 Å) relative to the neutral and a considerably elongated Ar**C**−**H** (1.136 Å) bond. In contrast, Ar**C**−CO of $\mathbf{20}^{\bullet+}$ is 1.609 Å, and the ArC−H bonds are fairly normal (1.090 Å). If radical cations are formed in the reaction, we thus predict that $\mathbf{20}^{\bullet+}$ should fragment more avidly than $\mathbf{19}^{\bullet+}$. Hydrogen atom abstraction from **19** and **20** would lead to the substituted benzylic fluorides, whereas fragmentation should lead to fluorotoluene (Scheme 2).

Scheme 2. Fragmentation of Radical Cations



Experimentally, photofluorination of **19** gave a mixture of **14** and **3** in an ∼5:1 ratio (67% total yield). On the other hand, as predicted, **20** affords relatively more fluorotoluene (benzylic fluorinated **20** to **3** form in a 2:1 ratio 41% yield). Coincidentally, in an electron impact mass spectrometry experiment, **19** yields an approximately 2.5:1 mixture of parent ion and the dioxolanyl cation fragment, mirroring the results in solution.[23] For additional support, we turned to the reputedly obligatory outer sphere electron transfer agent potassium dodecatungstocobaltate ($K_5Co^{III}W_{12}O_{40}$).[24] Oxidation of **20** by an outer sphere electron transfer mechanism should provide $\mathbf{20}^{\bullet+}$ selectively. If radical cations are involved in the photofluorination reaction, we should expect to find a similar ratio of benzylic fluorinated **20** to **3** by substituting TCB for $K_5Co^{III}W_{12}O_{40}$ in the absence of light. As it turns out, reaction of **20** with $K_5Co^{III}W_{12}O_{40}$ and Selectfluor in MeCN solvent provided an ∼2:1 ratio of benzylic fluorinated acetal to fluorotoluene, mimicking our earlier results with TCB. Thus, radical cations are almost assuredly involved in the reaction. We should also note that reaction of **20** using our copper(I) promoted fluorination conditions,[22] which have been established to operate through HAT, gave no fragmented product. Instead, only benzylic fluorinated product was observed.

Although a HAT mechanism would appear to be comfortably ruled out, discerning between ET and PCET pathways is often more difficult. Previously, it had been shown that TCB reacts with neat toluene under irradiative conditions through initial electron transfer followed by proton transfer to give substitution products.[25] Furthermore, formation of radical cation/anion pairs between irradiated TCB−aromatic systems is well documented, seemingly favoring an ET pathway.[26]

In conclusion, a photocatalyzed protocol for the mild, regioselective monofluorination of benzylic compounds has been reported. This system operates to afford a number of electronically and sterically diverse benzylic fluorides with potential medicinal and agrochemical value. Preliminary evidence for the involvement of radical cations in our reaction has helped to confirm these species as promising intermediates for halogenation reactions. Continued work will seek to elucidate the precise mechanism of this photofluorination system in tandem with the application of this method for the synthesis of complex fluorinated molecules.

■ ASSOCIATED CONTENT

Supporting Information

Includes NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

T.L. thanks the NSF (CHE-1152996) for support. S.B. thanks Johns Hopkins for a Gary H. Posner Fellowship.

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