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Hydrogen Bond Directed Photocatalytic Hydrodefluorination; Overcoming Electronic Control

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ABSTRACT: The photocatalytic C–F functionalization of highly fluorinated arenes is a powerful method for accessing functionalized multifluorinated arenes. The decisive step in the determining regioselectivity in fluorine functionalization is fluoride fragmentation from the radical anion of the multifluorinated arene. To date, the availability of regioisomers has been dictated by the innate electronics of the fluorinated arene, limiting the synthetic utility of the chemistry. This study investigates the remarkable ability of a strategically located hydrogen bond to transcend the normal regioselectivity of the C–F functionalization event. A significant rate acceleration is additionally observed for hydrodefluorination of fluorines that can undergo intramolecular hydrogen bonds that form 5-8 membered cycles with moderately acidic N–Hs. The hydrogen bond is expected to facilitate the fragmentation not only by bending the C–F bond of the radical anion out of planarity, but also by increasing the exothermicity of the fluoride extrusion step through protonation of the naked fluoride. Finally, the synthetic utility of the method is demonstrated in an expedited synthesis of the trifluorinated α -phenyl acetic acid derivative required for the commercial synthesis of Januvia, an anti-diabetic drug. This represents the first synthesis of a commercially important multifluorinated arene via a defluorination strategy, and is significantly shorter than the current strategy.

INTRODUCTION

Multifluorinated arenes are proving to be an important class of molecules for materials,¹ pharmaceuticals,² agrochemicals, and catalysts⁴ (Scheme 1a). There are no known natural sources of fluoroarenes,⁵ and despite the enhancements they provide, their syntheses can be extraordinarily difficult. To our knowledge, every commercially interesting multifluorinated arene is currently produced using the halex process or the Balz-Schiemann reaction, such as that seen in the synthesis of Januvia (Scheme 1b). The length of the synthesis stems not only from the difficulty of forming C-F bonds, but also from controlling the regioselectivity, often requiring the installation and removal of activating or deactivating groups. While recent developments in methodology have made accessing mono-fluoroarenes significantly more tractable,⁶ they have not solved the problem of multifluorinated arenes. This is because they either rely on converting pre-installed functional groups (i.e., halides or metals), or the directed substitution of C-H bonds (Scheme 1c, right). However, in the case of multifluorinated arenes, the selective installation of the necessary functional groups simply shifts the difficult steps to an earlier point in the synthesis. While directed functionalization avoids this issue, it is generally limited to ortho functionalization of the directing group and thus, only partially solves the problem.

In contrast to selective fluorination, perfluorination of the arenes, in which every C–H has been replaced with a C–F, is readily accomplished on a commercial scale, and completely eliminates the necessity of an arduous selective fluorination sequence.⁷ The challenge of synthesizing multifluorinated arenes is thus shifted toward selective C–F functionalization or reduction (Scheme 1c, left). If developed successfully, the empowerment of using this approach is manifold, since each fluorine has the potential to be functionalized. This potential has been recognized for some time, and has been championed

by others,⁸ though there are many challenges associated with C–F functionalization that have hindered its development.

Scheme 1. Multifluorinated Arenes, Current Technology, Novel Approaches



An example of these challenges is that oxidative addition into the short and strong C–F bond is challenging (for C–F of C_6F_6 , 1.3250 Å,⁹ 145 kcal/mol¹⁰). Furthermore, if oxidative addition is successful, many catalysts form strong metal–F bonds which can lead to sluggish catalytic turnover.^{8a}

In 2014, we introduced the photocatalytic hydrodefluorination reaction¹¹ (photo-HDF), which circumvented many of the aforementioned issues. Specifically, we showed that facile hydrodefluorination could be induced when an Ir-based photocatalyst, tertiary amine, and visible light were combined. Fundamentally, the reaction is believed to proceed via single electron transfer from the photocatalyst to the perfluoroarene (**A**, Scheme 2), to give a perfluoroaryl radical anion (**B**). The radical anion then undergoes C–F fragmentation to neatly generate a perfluoroaryl radical (**C**) which undergoes hydrogen atom transfer from the amine (or its radical cation) to give the hydrodefluorination (HDF) product (**D**).

The photocatalytic reductive fragmentation of an otherwise inert fluorine bond is proving to be a generally effective strategy. Recently Hashmi¹² has shown that the photocatalytic electron transfer and fluoride fragmentation strategy can be used to not only engage difluorostyrenes, but also to facilitate C–H functionalization of aryl amines.¹³ Jamison¹⁴ has shown that it can even be used to activate the otherwise inert SF₆. Furthermore, Zhang recently demonstrated that even nonprecious metal dyes can facilitate the photo-HDF reaction, in which he highlighted the importance of the secondary interactions of the catalyst and substrate to accomplishing the reaction.¹⁵

Scheme 2. Working Mechanism of Photo-HDF



Returning to the problem of multifluorinated arenes, we have previously demonstrated that the perfluoroaryl radical is a powerful intermediate for the functionalization of perfluoroarenes, which can elicit C-F alkylation,¹⁶ arylation,¹⁷ and alkenylation.¹⁸ While the perfluoroaryl radical has proven competent for cross-coupling, the inherent limitation is the regioselectivity of the C-F fragmentation event. Despite this fragmentation being generally regioselective, it is dictated by the intrinsic electronics of each substrate, ^{10,19} and therefore has until now been an obstinate limitation to the photocatalytic C-F functionalization strategy. In order for the field to advance, strategies are needed which provide alternative C-F fragmentation regioselectivities from the same motifs. With this goal in mind, we began to contemplate the rudiments of the C-F regioselectivity in the photo-HDF and C-F functionalization reactions, and specifically, how they might be subverted.

The structure of the perfluoroaryl radical anion of hexafluorobenzene is known to be nonplanar, in which the C–F bonds are contorted out of the plane of the ring.²⁰ In fact, the fragmentation process is greatly accelerated by this nonplanarity, because it allows for significant mixing of the π^* and the C–F σ^* orbitals, effectively lifting the otherwise symmetry forbidden intramolecular electron transfer. Given the importance of both the directionality and shape of the C–F σ^* orbital for overlap with the arene π^* orbital, it stands to reason that perturbation of either the length or direction of σ^* orbitals of the C–F bonds will thus influence the likelihood of the bond's fragmentation from the radical anion which is formed upon electron addition.

We postulated that the C–F bonds at locations which do not typically undergo fragmentation could be enticed to do so by the strategic positioning of an acidic proton.²¹ Literature suggests that while hydrogen bonding with organofluorines is a weak interaction,²² hydrogen bonding with the fluoride ion is strong.²³ Unfortunately, this provides little insight with respect to the ability of an organofluorine radical anion, which possesses an intermediate amount of negative charge, to engage in hydrogen bonding. Additionally, since solvation of fluoride is a highly exothermic process,²⁴ it was expected that the fluoride fragmentation event would become more exothermic because the newly formed fluoride would already be engaged in a hydrogen bond.²⁵

RESULTS AND DISCUSSION

We initiated our study with *N*-acetylated tetrafluoropyridine, **4a**, which was subjected to standard photo-HDF conditions, which consisted of catalytic amounts of $(fac-Ir(ppy)_3)$ (tris[2phenylpyridinato- C^2 ,*N*]iridium(III)), and three equivalents of DIPEA (diisopropylethylamine) (eqn 2, Scheme 3). We observed smooth and efficient HDF with complete C3 selectivity as confirmed by an X-ray structure of the product, in contrast to the electronically favored position, C2. When the nitrogen of the substrate was methylated (**3b**), removing the acidic NH, and subjected to the same reaction conditions, it underwent photo-HDF exclusively at C2, though notably more slowly (eqn 3).²⁶ Methylation of **4a'** allowed direct comparison to **3b'** and confirmed the correlation of regioselectivity to the presence or absence of the acidic proton.²⁷

Deuterium labeling studies suggest that neither the acidic proton (eqn 4) nor the solvent (eqn 5) were serving as the H-atom source.





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This further suggests the importance of NH is to undergo hydrogen bonding with the fluoride, rather than serving as an Hatom source. Previously, we have shown that the amine (or its radical cation) was the source of the H-atom in the photo-HDF,¹¹ and these results are consistent with our previous observations.

This result is consistent with the idea that manipulation of the C–F σ^* orbital is a viable strategy for obtaining alternative regioselectivity in the reductive fragmentation. This is consistent with Shteingarts'²⁸ observations that zinc ions accelerated the dissolving metal-HDF with *N*-acetylated polyfluoro-amines, in which it was proposed that zinc ion coordination of the acetyl group and the ortho fluorine both accelerate the reaction and alter the regioselectivity. Given both the mild reaction conditions of the photo-HDF and the ubiquity of acidic protons within polyfluorinated molecules of interest, we surmised that this chemistry has significant potential to alter how multifluorinated arenes are synthesized. We set about studying the reaction to try to understand the limitations and requirements.

Scheme 4. Directly Attached Directing Groups



Substrates such as **4** are rapidly synthesized from inexpensive pentafluoropyridine in two steps, and we initially explored the scope of directing groups in which the acidic proton is directly attached to the tetrafluoropyridine ring (Scheme 4). The steric demand of the acetyl group has little impact on the isolated yield (**4a'-d'**), which uniformly gave high yields. We found that benzoyl amides also generally served to direct the HDF event. The HDF event took place smoothly for both electron rich- (**4e'-g'**), neutral- (**4h'-i'**) and electron poor amides (**4j'n'**). In the case of the nitro-substituted benzoyl amide, the reaction failed to take place. This likely resulted from competitive quenching of the photocatalyst by the nitroarene motif which has previously been observed.²⁹

At low conversion (ca. 20%), an average rate was determined and a pseudo-Hammett plot was constructed (eqn 6, Figure 1). A positive ρ value (1.24) is consistent with a buildup of negative charge during the rate determining step (RDS). This result indicates that the RDS is fluoride fragmentation, in which partial proton transfer to a fluoride occurs, and explains the prominent role the acidity of the hydrogen bond donor plays in the reaction outcome. We next explored the type of H-bond donors which were competent at facilitating the directed photo-HDF reaction. In general, only N–H groups were found to be suitable, though





Figure 1. A pseudo-Hammett plot of the directed photo-HDF reaction of tetrafluoropyridine. The average rate at ca. 20% conversion is plotted against the σ -para values.³⁰

others were explored.³¹ Given the prevalence of N–H bonds in pharmaceuticals and other polyfluorinated arenes of interest, we explored a number of common motifs (Scheme 5). We were pleased to see that an electronically diverse range of aniline substituted tetrafluoropyridines underwent smooth HDF ($5a^{27}$ -e'). However, aliphatic amino pyridine 5f' was unreactive, possibly stemming from decreased acidity or inappropriate conformation due to the aliphatic nature of the substituent. Tetrafluoropyridine could be substituted with other important heterocycles such as pyridine to give partially fluorinated bipyridine, 5g', after HDF. Additionally, a BOC-protected amine (5h) serves as an excellent directing group. Given the frequency of these motifs in pharmaceuticals and

Scheme 5. Exploration of other directing groups for tetrafluoropyridine



agrochemicals, the directed photo-HDF reaction may be useful for late stage defluorinations, and rapid substrate diversification in structure-activity relationship (SAR) studies.

Next, we investigated the generality of the directed photo-HDF with respect to the polyfluoroarene (Scheme 6). We were pleased to see that the acetamide substituent could effectively direct the HDF on perfluorinated derivatives to give a single regioisomer, including benzonitrile ($6a^{27}$), trifluorotoluene³² ($6b^{27}$), benzoate ($6c^{27}$), and even benzene ($6e^{2}$). In the case of pentafluorobenzene derivative 6e, the initial mono-HDF was the directed product, but was rapidly consumed to give the di-HDF product ($6e^{2}$).

Scheme 6. Exploration of other polyfluoroarenes in the directed photo-HDF reaction



a. N-ethyl morpholine used instead of DIPEA. b. NMR yield. c. No conversion. d. See ref. 32.

We next investigated trifluoroacetyl as a directing group (6f-6j), which is attractive both because of its potential to acidify the NH, as well as its facile removal under basic conditions. While it worked well for several substrates, we found that some failed to form any product (6f, 6g and 6j). In the case of 6f and 6g, the N-H was sufficiently acidified to be deprotonated by DIPEA, which retarded the rate of reaction (6f is nearly 4 pKa units more acidic than 4a).³³ The consequence of N-H deprotonation would be a more difficult electron transfer to the perfluoroarene since the original LUMO would be occupied by the electrons originally located in the N-H bond, preempting electron transfer and fluoride fragmentation. Furthermore, the amine reductant would be protonated, preventing it from serving as the reductant. We probed this possibility by use of N-ethyl morpholine as the amine reductant, which is estimated to be nearly 3-4 pKa units less basic (MeCN) than DIPEA, as the reductant.³⁴ While the photo-HDF reaction of 6f still failed, the reaction of 6g took place smoothly, giving 6g' in 75% yield. This result indicates that deprotonation of the directing group is one resolvable issue

that can arise in the photo-HDF reaction. The reason for the failure of 6j, is not clear at this time.

Substrates $6l^{27}$ and $6m^{27,32}$ show that even a simple amino group can often serve to facilitate the HDF event, provided there is an acidifying group attached to the ring ($6l^{2-6n^{27,32}}$). However, in the case of 4-amino pyridine (6k) and perfluoroaniline (60) the reaction failed. Currently, the reasons for the failure of these substrates is abstruse.

Our working hypothesis of the reaction is that the lifetime of the radical anion is relatively short, and productive fragmentation must compete with unproductive back electron transfer. Therefore, in order for the hydrogen bond to perturb the regiochemical outcome of the photo-HDF reaction, it must either be operative at the time of radical anion formation, or commence rapidly after the electron transfer event. Hence, the fivemembered cyclic intramolecular hydrogen bond between the acidic proton and the neighboring fluoride would be ideal for achieving the directed HDF. Whether more remote hydrogen bond donors could effectively accelerate the fluoride fragmentation was yet to be seen. Consequently, we opted to systematically explore this by inserting one or more atoms between the acidic N–H and the arene ring, enlarging the cyclic transition state from five to eight members.

We next expanded our studies to include substrates which would form a six-membered intramolecular hydrogen bonding ring (Scheme 7). Specifically, perfluorobenzoylamides that can be synthesized in 1-step via amine addition to the perfluorobenzoyl chloride, were subjected to the HDF conditions (**7a-h**). We found the perfluorobenzoyl amides, **7**, to be more complex than other systems, in which several different reaction pathways could be operative, and conformational changes after one HDF event often facilitated the next HDF event. Careful monitoring of the reaction by ¹⁹F NMR revealed that simple aliphatic benzoyl amides (**7a**) first give the electronically controlled para-HDF product, which is rapidly consumed to give the di-HDF product in reasonable yield (**7a**'). Curious-ly, aniline derived amide **7b** underwent directed HDF, and gave a temperature dependent product. At 45 °C the





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59 60 ortho/para di-HDF product was obtained (**7b'**), whereas when the reaction temperature was reduced to room temperature, the ortho/ortho' di-HDF product was obtained $(7b'')^{27}$.

When the more sterically congested amide 7c was subjected to the reaction, the ortho/ortho' di-HDF product 7c' was also obtained, even at 45 °C. Increasing the acidity of the N–H further accelerated the directed HDF and allowed the isolation of the mono-HDF product 7d' product in good yield (7d vs. 7e). Heteroaryl amides also served as good directing groups (7f' and 7g'). Substrates 7h-7j highlight the important role that temperature plays in dictating regiochemistry. Specifically, at the slightly reduced temperature (i.e. 23 °C) high yields of the directed di-HDF product was obtained.

In several cases, directed mono-HDF was rapidly followed by a secondary electronically controlled HDF, i.e. para to the carbonyl group (7b, 7e-7g). Still in other substrates, the product outcome had a clear temperature dependence, and the electronically controlled HDF could be avoided all together (7b-7d, and 7h-7j). We suspected that these divergent reaction outcomes were primarily due to conformational changes associated with the orientation of the directing group which occur after the first HDF event, and were precipitated by decreased steric repulsion about the carbonyl group upon substitution of the fluorine with hydrogen. The increased flexibility, in turn, could allow increased conjugation between the π -system of the carbonyl and fluoroarenes, which would lead to a lower lying LUMO, and therefore a more facile electron transfer to the arene. However, it would place the N-H in the plane of the fluoroarene ring, or nearly in plane, preventing the key C-F deformation needed to accomplish directed-HDF. Consequently, electronically controlled fragmentation would dominate. We postulated that it might be possible to find an amide with a structure such that even after the first HDF event, it would not be prone to undergo the hypothesized conformationally dictated electronic HDF. Accomplishing this could provide an unprecedented level of control. Such control is desperately needed if C-F functionalization is to become reality in the synthesis of multifluorinated arenes.

Lloyd-Jones and Booker-Milburn have shown that very bulky amides are prone to undergo solvolysis. The reason for this is facile N–CO bond rotation which results from steric decompression which occurs as the N rotates out of conjugation with the amide.³⁵ While our system was somewhat different, we hoped that a bulky amide could be used to more easily achieve the necessary out of plane N–H which we posited would lead to directed-HDF.³⁶ We synthesized sterically hindered amide **8a** (Scheme 8), which indeed provided excellent thermal control over the product distribution. At room temperature, the

Scheme 8. Directed HDF with sterically hindered amides.



reaction gave primarily ortho-HDF (eqn 7), along with a small amount of **8**". Simply heating gently (45 °C) and extending the reaction time, the same substrate could be enticed to undergo di-HDF to obtain the 2,6-di-HDF product, **8a**", in 87% (eqn 8). Finally, at 60 °C with 6.0 equivalents of DIPEA, we observed that the ortho/para/ortho' tri-HDF product could be obtained (eqn 9). Thus, the 2,6-dimethyl aniline derived amide (**8a**) is a very versatile substrate that can provide facile access to several fluorinated derivatives simply by modulating reaction temperature, time, and amine loading as the key reaction parameters.

While not every possible fluorination pattern of pentafluorobenzoic acid has yet been realized, collectively, these results highlight the versatility of the photocatalytic C–F reduction strategy. By judicious choice of (non)directing group, in just two synthetic steps from commercially available perfluorobenzoyl chloride, five different polyfluorination patterns³⁷ can be obtained in high yield, and is a realization of significant progress in our efforts to synthesize multifluorinated arenes.

We expanded our study of substrates which involved 6membered hydrogen bonds by exploring non-natural alpha amino acids derivatives (Scheme 9), which are rapidly synthesized via perfluoroarvlation of the oxazolone followed by the appropriate workup,³⁸ or in the case of 9d via the addition of nitromethane followed by hydrogenation.³⁹ We were pleased to see that the benzoyl protected amino acids (9a and 9b) underwent smooth photo-HDF, and that the HDF products were isolated in good yields. The ethyl ester derivative was isolated in high yield $(9c')^{27}$. Somewhat surprisingly, the HCl salt of the benzylic amine (9d) proved to be an excellent substrate, even if the reaction was somewhat sluggish due to its low solubility. Protonation of the amine was found to be essential for reactivity. Given the propensity for primary amines to undergo nucleophilic aromatic substitution with these types of arenes, it is particularly remarkable that not only did the protonation of the amine (HCl salt) serve as a protecting group, but also as an excellent directing group (9d').

Scheme 9. Exploration of 6-membered hydrogen bonding substrates (continued).



It is conceivable that the ammonium salt accelerates the electron transfer via electrostatic stabilization of the radical anion, in addition to the fluoride fragmentation. In contrast to previous examples, fluoride fragmentation would yield an overall neutral complex upon complete protonation of the leaving fluoride. We were also pleased to see the perfluoroaryl cyclic guanidine (**9e**), which is a motif that is under investigation as a potential therapeutic for Alzheimer's disease as a BACE-inhibitor,⁴¹ undergoes smooth directed-HDF to the product **9e'** in high yield. The ability to rapidly vary the fluorination pat-

tern will likely be helpful in lead optimization during discovery efforts involving fluorinated arenes.

We next investigated systems in which a seven membered hydrogen bond ring is formed (Scheme 10). The substrates are formed in a single step⁴² via the decomposition of the per-fluoroarylated Meldrum's acid enolate salts, which are commercially available as FAYE blocks (Fluoroaryl AcYl Equivalents).⁴³ As seen in smaller ring systems involving the tetra-fluoropyridine motif (i.e. **4a**, **5a**, and **9a**), only a single regioi-somer was observed in the directed-HDF reaction across a diverse range of directing groups, giving the trifluoropyridine in good isolated yields (**10a'-10f', 10d'**²⁷). Additionally, the glycine ethyl ester (**10g**) and benzonitrile aniline (**10h**) derived heptafluorotoluene underwent smooth directed-HDF to give hexafluorotoluene products (**10g'**²⁷ and **10h'**) in good yield and perfect selectivity.

Scheme 10. Exploration of 7-membered hydrogen bonding substrates.



We next investigated the benzoate series (Figure 2 and Scheme 11). In our experience, methyl pentafluorobenzoate is more prone to a second electronically controlled photocatalytic fragmentation event when compared to other perfluoroarenes.^{11,42} The second fragmentation takes place at the position ortho to the carboxy group. It is not surprising then, that when the preferred site of photocatalytic functionalization is substituted with a carbon substituent para to the ester, the electronically controlled HDF still takes place at a reasonable rate. Thus, substitution of the para position of the benzoate system with a directing group presented an opportunity for an internal competition experiment. We investigated this by conducting an experiment to compare the relative rate between the directed- and electronically-controlled HDF and is reflected in the regioselectivity (eqn 10, Figure 2). When the log of the ratio of the directed-HDF product (F2a'-d') to the electronically controlled-HDF product (F2a"-d"), obtained at 45 °C, was compared to the Hammett values, a linear correlation with a positive slope (ρ =1.027) was observed. This finding is consistent with our earlier Hammett study within the five membered series (Fig. 1) which also indicated negative charge build up in the transition state. When R is an electron releasing group, the electronically controlled product (**F2a''-d''**) is dominant. In contrast, electron withdrawing substituents such as a nitrile accelerate the directed-HDF reaction (**F2a'-d'**). A positive ρ value suggests that negative charge increases in the transition state and explains why the acidity of the proton plays an important role in determining which fluorine undergoes fragmentation.



Figure 2. A linear free energy relationship of the HDF regioselectivity as a function of σ_p^- Hammett values⁴⁴ in the methyl benzoate series with a remote directing group.

We further explored a range of directing groups within the methyl benzoate series in which a seven membered hydrogen bond is formed (Scheme 11). Again, we observed a significant temperature effect, similar to what we had previously observed for the perfluorobenzoyl substrates (Schemes 7 and 8). For instance, when **11f** was used in the Hammett study at 45 °C, the electronically controlled product was favored (**F2b''** 1.2:1, Fig. 2). However, by dropping the temperature to 23 °C, the directed-HDF product was formed almost exclusively (94%, **11f'**, Scheme 11). Thus, the photo-HDF reaction

Scheme 11. Exploration of benzoate motif



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59 60 of all of the benzoate substrates was performed at room temperature, in order to favor the directed-HDF product.

Finally, we briefly evaluated the ability to perform the directed photo-HDF when the directing group formed an 8membered hydrogen bonding cycle (eqn 11). While the reaction was noticeably slower, and did not reach completion, it did give the directed-HDF product exclusively, demonstrating the ability to use even relatively remote acidic groups to facilitate the reaction. This motif is found in a number of aryloxyacetic acid drugs such as ethacrynic acid, and fenofibrate, and represents a major class herbicides such as 2,4-D, and fluoroxypyr. Thus, the directed photo-HDF reaction may be helpful in accelerating compound discovery that encompasses future elaboration of this motif toward fluorinated congeners.



The reaction may also prove useful for larger scale production. Two obvious issues are the batch nature of the reaction and the scarcity of rare earth metals, iridium in this case, that are used in the photocatalyst. First, we¹¹ and countless others^{14,45} have demonstrated that almost any photo-HDF reaction can be transposed from batch to flow methodology, usually with improved kinetics. Second, given that the reaction is triggered by an electron transfer, it is likely that there are numerous other catalysts which could facilitate the photo-HDF reaction and relieve the iridium issue altogether.¹⁵ Until that is demonstrated, we wanted to probe the robustness of the photocatalytic system for this reaction (eqn 12). In the standard reaction conditions, we used relatively low catalyst loadings (0.25 mol%), although presumably much lower Ir-loading would be needed in order for the process to be amenable to scaling. Remarkably, with reduced photocatalyst loading but otherwise normal reaction conditions (12.5 ppm or 0.00125 mol% Ir(ppy)₃), we observed 64% assay yield, giving 52,500 catalytic turnovers (TONs), suggesting that it may be possible to use even an Ir-based photocatalyst to accomplish a commercially important hydrodefluorination.



Having developed a solid understanding of the directed and undirected photo-HDF reaction, we wanted to demonstrate the potential of the reaction, and more generally the potential of the C–F functionalization/reduction strategy to facilitate access to important multifluorinated arenes. As a target, we chose to synthesize the key starting trifluorophenyl acetic acid (**12c**, Scheme 12) which was utilized by Merck and Codexis in the third generation synthesis of the anti-diabetic drug, Januvia (sitagliptin).⁴⁶ While the end-game of the Januvia synthesis is truly elegant, the synthesis of the key acid **12c** is wanting, and thus, represents an ideal platform to demonstrate the utility of our methodology.⁴⁷

We began our synthesis with 3-chloro-tetrafluorobenzoyl chloride⁴⁸ (12a, Scheme 12) which contains all of the neces-

sary fluorines in the desired positions and is likely derived in just a few steps from benzonitrile.⁴⁹ Three main objectives needed to be accomplished, homologation of the acid, photocatalytic dechlorination, and directed photocatalytic defluorination. The homologation step can come before or after the dehalogenations, as both lead to formation of the product.³ We elected to first convert the benzoic acid derivative to an acetic acid derivative by forming the α -diazo ketone, which was subjected without isolation to a silver catalyzed, one-step Wolff rearrangement-amidation sequence to arrive at 12b in 97% crude vield. We were now positioned to perform the key photocatalytic di-dehalogenation (HDX) reaction, in which we needed to remove the chlorine at the 3-position and the fluorine at the 6-position. Without any chromatographic purification, the material was taken into the photocatalytic-HDX reaction. Based on our experience, we expected the chlorine to fragment first,^{11,16-17,51} which would lead to an unsymmetric intermediate. Fluorines at both the 2 and the 6 positions could undergo HDF. We hoped that the reduction of the chlorine would electronically activate the fluorine at the 6-position, as this had been previously seen in the benzene series.^{11,15} After full conversion, the solvent was removed and the crude material refluxed in aqueous HCl. Purification via acid/base workup removed the photocatalyst, and the aniline to afford the analytically pure product 12c in 95% yield, and 92% overall yield from a commercially available benzoyl chloride.

Our telescoped synthesis required no column chromatography and gave an overall yield of 92% yield from **12a**, and is the most expedient synthesis to this important trifluorinated acid. To our knowledge this is the first use of a defluorination strategy to access a commercially interesting multifluorinated arene, which we hope will inspire others to incorporate defluorination as a strategy to access important multifluorinated compounds. Scheme 12. Synthesis of key fluorinated starting material for Januvia



CONCLUSIONS

We have demonstrated and explored the ability of hydrogen bonding to accelerate and alter the regioselectivity of the photocatalytic-HDF reaction. This work provides access to complimentary regioselectivity compared to the previously disclosed electronically dictated outcome, which is key for furthering the synthetic strategy of C–F functionalization. Though the reaction takes place through a photocatalyzed outer sphere electron transfer, which to some extent may limit our ability to control the reaction outcome, we have shown that careful planning, and utilization of the commonly encountered acidic N–H, can allow control over the reaction outcome, even when many isomers are possible. Furthermore, this strategy may potentially be applied to other radical anion fragmentation chemistry to help overcome the normal selectivities.

ASSOCIATED CONTENT

Supporting Information. Spectra, X-ray crystal structures, procedures, and additional experiments are contained in the supporting information. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare a competing financial interest in that they hold a patent, United States Serial No.: 62/043,650 concerning the structure and method for the Meldrum's acid adducts.

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