Molecular Sculpting; a Multipurpose Tool for Expedited Access to Various Fluorinated Arenes via Photocatalytic Hydrodefluorination of Benzoates

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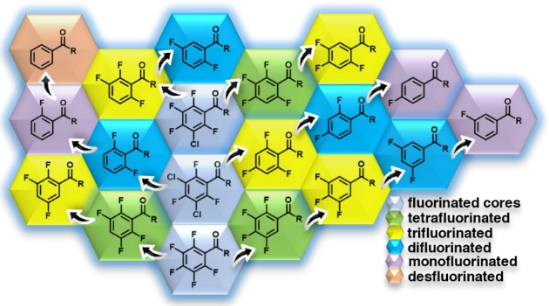


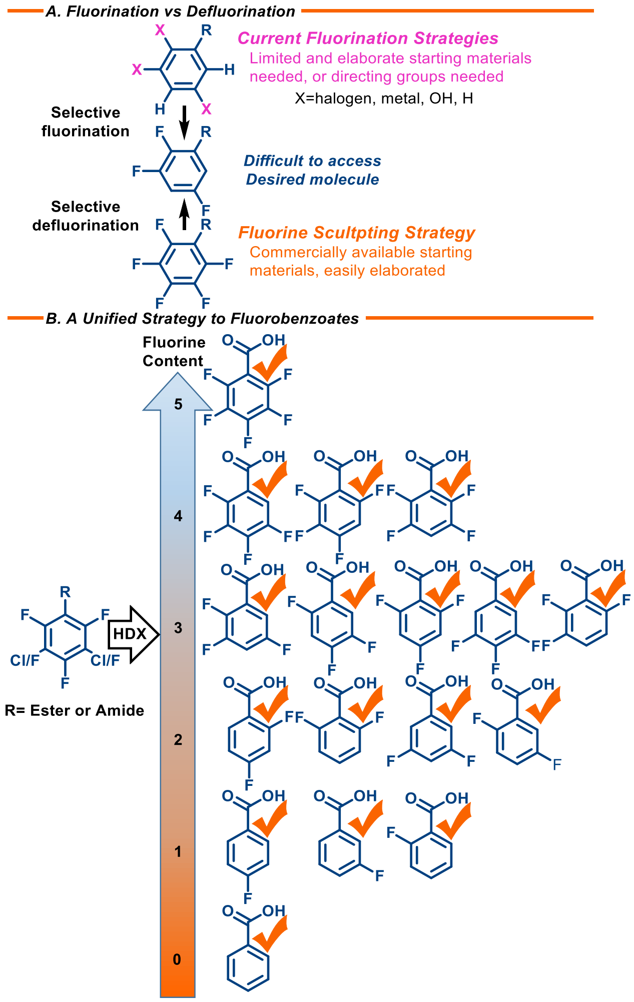
ABSTRACT: Starting with highly fluorinated benzoates, we develop the directed photocatalytic hydrodefluorination (HDF) of fluorinated aryl benzoates and demonstrate its synergistic use with other HDF strategies, along with C–H arylation, decarboxylative coupling and decarboxylative protonation to access most fluorination patterns found in benzoate derivatives and by extension, benzene derivatives *via* a molecular sculpting approach. Mild reaction conditions and excellent regioselectivity make the approach ideal for synthesis. This approach provides access to 16 benzoate derivatives with different fluorination patterns from just a couple of highly fluorinated, commercially available benzoic acids. We synthesize key intermediates or the API for sitagliptin, diflunisal, and other pharmaceutically important molecules. Importantly, we provide key insights into relative rates of defluorination and strategies to alter these rates. We provide demonstrations of the synergistic use of HDF and related technologies to rapidly enhance the synthetic complexity of these simple commercially available perfluoroarenes into complex partially fluorinated molecules.

INTRODUCTION

Organofluorine motifs have become an essential component in pharmaceuticals and agricultural products.[1] Despite their frequent use, fluorinated arenes are unnatural and must be synthesized. Many fluorination patterns require intense synthetic processes, with subtle alterations in the fluorination pattern often requiring entirely new synthetic sequences. This hampers exploration of fluorinated chemical space. Common protocols to access multifluorinated arenes often utilize either the halogen exchange reaction (halex process) which requires extreme temperature or the Balz-Schiemann reaction which allows aryl amino groups to be converted to the corresponding aryl fluoride via the corresponding diazonium. Usually, the diazonium must be isolated as the BF_4^- salt, significantly increasing the risk of explosion. Not surprisingly, recent efforts have focused on the modernization and innovation of fluorination strategies, including catalytic fluorination of prefunctionalized arenes,[2] directed C−H fluorinations,[3] strategies to catalyze the halex reaction,[4] and improvements to the diazotization techniques (**Scheme 1A**).[5] Although these strategies offer, in principle, the possibility of achieving multifluorinated arenes, in practice this remains challenging, which stems from the synthesis of appropriate precursors. Alternatively, in the case of C–H fluorination, a lack of versatility in terms of the regioselectivity hampers utilization.

An alternative approach to selective fluorine installation is selective fluorine removal (or functionalization) from a fully or highly fluorinated molecule. This can be achieved using perfluoroarenes, which unlike partially fluorinated arenes, are synthesized more readily and are commercially available. Complete fluorination- though an intense process, removes any selectivity issues, is straightforward, and is accomplished industrially on a large scale. Thus, selective defluorination could be a convenient approach to multifluorinated arenes, akin to fluorine sculpting. Furthermore, if this technology is realized and coupled to C–H functionalization iteratively could lead to unprecedented achievements in the levels of complexity of the organofluorines that can be synthesized.[6]

Scheme 1. Fluorination strategies



The challenge then shifts from *making* a C–F bond to selectively *breaking* just one of many C–F bonds. This idea has been developed by many researchers over the years, and while attractive, still faces challenges.[7]

Previous efforts have been fraught with difficulty. Site-selectivity remains a major challenge in metal-catalyzed C–F bond functionalizations, and once activated, many transition metal complexes form strong metal–F bonds often resulting in sluggish catalytic turnover that requires high energy reductants that form stronger M–F bonds (i.e., Si–F).[8] Among C–F functionalization reactions, a mechanistically unique and increasingly broad class of reactions is the photocatalytic reductive fragmentation of C–F bonds, which complements other C–F bond functionalization methods.[7a, 7c, 8b, 9] Previously, we showed that visible light and a photocatalyst could be used to accomplish reductive fragmentation, giving rise to the photocatalytic HDF (photo-HDF) reaction, which displayed mild reaction conditions and broad functional group tolerance. Importantly, visible light provided the driving force needed to break the strong C–F bonds via an outer sphere electron transfer process[10] which prevented the formation of problematic M–F bonds. Thus, our group focused on the development of the photocatalytic reductive fragmentation strategy and has shown that under very mild conditions aryl C–F bonds can be selectively substituted with H,[11] alkyl,[12] alkenyl,[13] prenyl,[14] and aryl[15] groups. Taken together with Hashmi's[16] and Bissember's[17] aminomethinylation, this strategy significantly expands accessible fluorinated systems. Others have applied this strategy to related fluorinated systems and the photoredox approach has proved productive in benzylic defluorination[18] and allylic systems[19] as well. However, a relatively low lying LUMO is a prerequisite for electron transfer, suggesting that this strategy will not be extendable to simple aliphatic fluorides that do not possess such a vacant orbital.

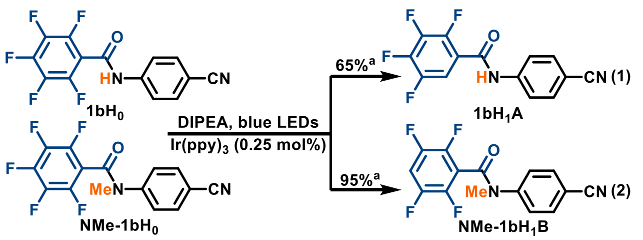
In our efforts to develop the photocatalytic C–F functionalization we discovered that within polyfluoroarenes the normal, or electronically controlled, C–F regioselectivity could be completely altered by the incorporation of an intramolecular hydrogen bond between an acidic N–H and an aryl–F situated in an ortho position on the ring.[20] Unfortunately, after publication of our findings we discovered that some of the spectra had been modified by one author, making it impossible to know the scope of the reaction and the conclusions uncertain. Thus, we retracted the paper.[20] However, at its root we believed the concept was valid and we wished to carefully demonstrate this concept as it was expected to be an important tool in the arsenal of C–F functionalization reactions.

Because of its synthetic versatility, we chose to focus our attention on the benzoate motif. Herein, we carefully develop the photocatalytic *directed* HDF (photo-d-HDF) of polyfluorobenzoic acid derivatives and demonstrate that, when used in concert with a handful of other related reactions, it can provide diverse access to fluorinated chemical space. The fluorinated congeners of benzoic acid which we can access by application of this strategy are shown in **Scheme 1B**. Importantly, while existing methods work well to obtain some of these fluorinated benzoates (i.e., highly, and sparsely fluorinated), the partially fluorinated benzoates (i.e., 2-3 F) are more difficult to access. The fluorine sculpting strategy can be rationally applied to access all these analogs. The value of the defluorination strategy is enhanced by coupling it to other chemical technologies, and we demonstrate the symbiosis through the expedited synthesis of several medicinally relevant molecules.

RESULTS AND DISCUSSION

We posited that rationally placed hydrogen bonds could accelerate the fragmentation of fluorides that were not inherently favored by orbital overlap (i.e., electronically controlled) in the radical anion which is formed after electron transfer from the photocatalyst. Furthermore, we believed that the hydrogen bond would help bend the C–F bond out of planarity accelerating mesolytic cleavage and stabilize the newly formed fluoride ion. Key experiments demonstrate the critical nature of a moderately acidic intramolecular hydrogen bond in facilitating a switch in regioselectivity of the photo-HDF reaction (**Scheme 2**). The pentafluorobenzamide with an N–H leads to ortho-HDF (eqn 1). In contrast, when the N–H is replaced with N–Me (eqn 2), HDF occurs at the para-position. Thus, we re-explored this chemistry in hopes of fully understanding its nature and limitations and to demonstrate its synthetic utility when used in conjunction with the photo-HDF to access the various fluorinated motifs. Herein, we identify specific conditions that allow remarkable synthetic control over the order and location of hydrodehalogenation. The conditions utilize just a handful of highly similar substrates to nearly completely enumerate the fluorinated chemical space. We anticipate this knowledge will streamline exploration of fluorinated chemical space.

Scheme 2. Hydrogen bonding alters the regioselectivity



^{a}Reaction conditions: *fac*-Ir(ppy)$_3$ (0.25 mol%), MeCN (0.1 M), Ar, blue LEDs, DIPEA (1.2 equiv), 65 °C.

Figure 1. The fluoroarene cores and directing groups studied and nomenclature system

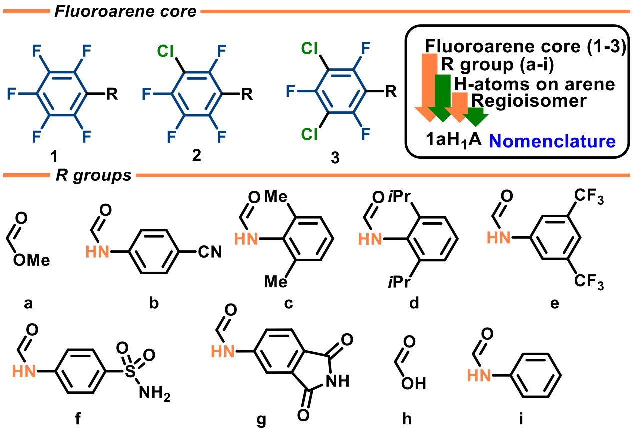
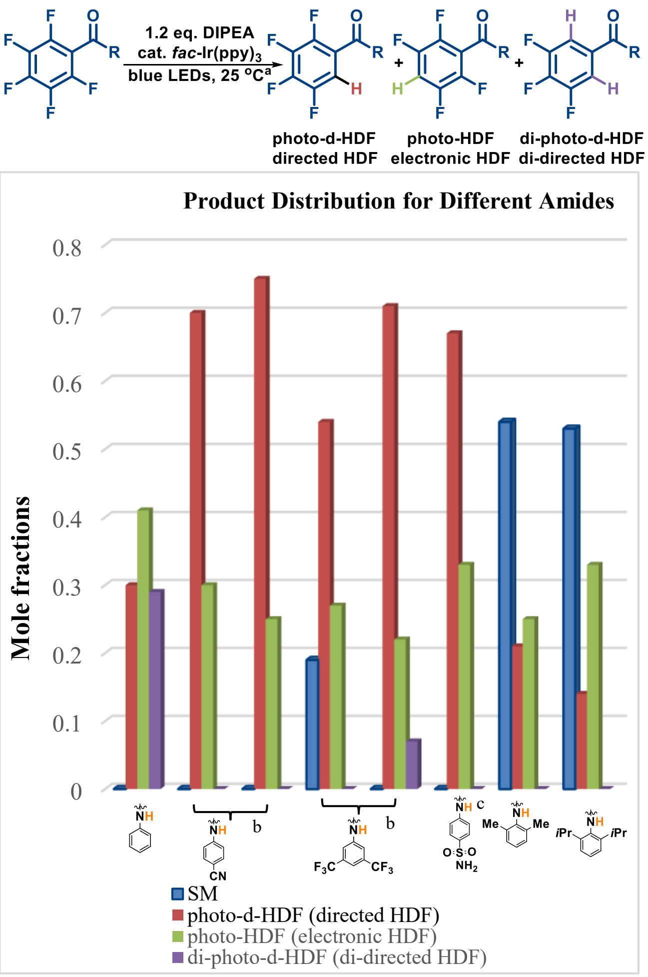


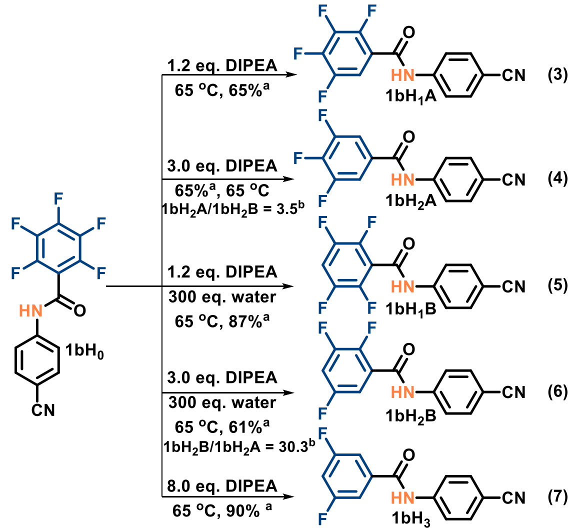
Figure 2. Product distributions as a function of amide



Mole fractions based on 19F NMR. ^{a}Conditions same as Eqn 1 except at 25 °C. ^{b}Reaction run at 65 °C. ^{c}DMSO was used as a co-solvent (MeCN:DMSO=1:1).

Our study involved just three different fluorobenzoic acid cores (**Figure 1**, top), which are commercially available and derived from the halex process, with **2** and **3** being the most prominent by-products of the synthesis of **1**.[21] The benzoic acid cores were then functionalized to give their corresponding amides or esters (**Figure 1**, bottom). Our studies explored the effects of these groups on the regioselectivity and reactivity of the photo-HDF reaction, then strategically employed them to achieve unique multifluorinated patterns. In some cases, the starting material is not obvious upon inspection of the product. Consequently, we have utilized a nomenclature system that indicates the core (**1-3**), the functional group **R** (**a-h**), the number of hydrogens (**H$_{0\text{-}5}$**), and indicates an isomeric form of the product when more than one exists (**A** and **B**). We initiated our studies using conditions previously established for the electronically controlled photo-HDF reaction and explored the effect of the amide group.[11] Specifically, we used diisopropyl ethyl amine (DIPEA) as our reductant, blue LEDs, and 0.25 mol% *fac*-Ir(ppy)$_3$, (**Figure 2**). We investigated both electron poor and sterically congested amides. *Para*-cyano substituted (**1bH$_0$**), bis-*meta*-CF$_3$-substituted (**1eH$_0$**), and para- sulfonamide (**1fH$_0$**) preferred the directed-HDF *ortho*-product over the electronically controlled *para*-product which was the preferred product of the sterically congested amides (**1cH$_0$** and **1dH$_0$**). The *para*-cyano gave the best ratio of directed to electronic product and seemed to be insensitive to temperature increase whereas the bis-*meta*-CF$_3$-substituted amide (**1eH$_0$**) tended towards the di-HDF product. Thus, for many of our following studies we primarily used the nitrile derived amide. Indeed, with the *para*-cyano amide, the photo-d-HDF product was dominant, **1bH$_1$A** (Eqn 3, **Scheme 3**), yielding the ortho-HDF product in 65% isolated yield. With increased DIPEA loading and more reaction time, a second HDF event took place which occurred at the other ortho position giving a 65% yield of **1bH$_2$A**, with only a minimal amount of 2,4-di-HDF product being observed (3.5 rr, eqn 4). We found, however, that water played a critical role in the reaction and could be conveniently used to intentionally disrupt the directed-HDF and accelerate the electronic-HDF (*vide infra*). Presumably, the presence of water disrupts the relatively fragile intramolecular hydrogen bond within the organofluorine thereby increasing the barrier to mesolytic fragmentation of the ortho fluoride from the radical anion.[22] Further, the coordination of water may induce other structural changes that shift the preference towards the para-fluorine. Finally, the water molecules are free to solvate any of the fluorides from about the ring, and as a result, seems to mostly just accelerate the electronically preferred fluoride fragmentation.[23] When all solvents and reagents were dried prior to use, the directed product dominated (photo-d-HDF), but when just a few equivalents of water were added to otherwise unchanged conditions, we observed a return in the C–F fragmentation regioselectivity to electronic control (photo-HDF), which peaked around 300 equivalents of water. Under these conditions, the reaction gave us the electronically dictated para-HDF product, **$1bH_1B$** (Eqn 5) in excellent yield, 87%, despite having a directing group attached. Heating this reaction and increasing the DIPEA equivalents led to a second defluorination event which occurred at the ortho position giving us the 2,4 di-H product **$1bH_2B$** (61%, eqn 6). In contrast, under dry conditions with excess DIPEA, the acidic amide will undergo tri-HDF to give **$1bH_3$** in excellent yield (90%, eqn 7), which forms by directed-HDF, followed by directed- HDF, and ultimatly electronic-HDF.

Scheme 3. Exploring the HDF reaction



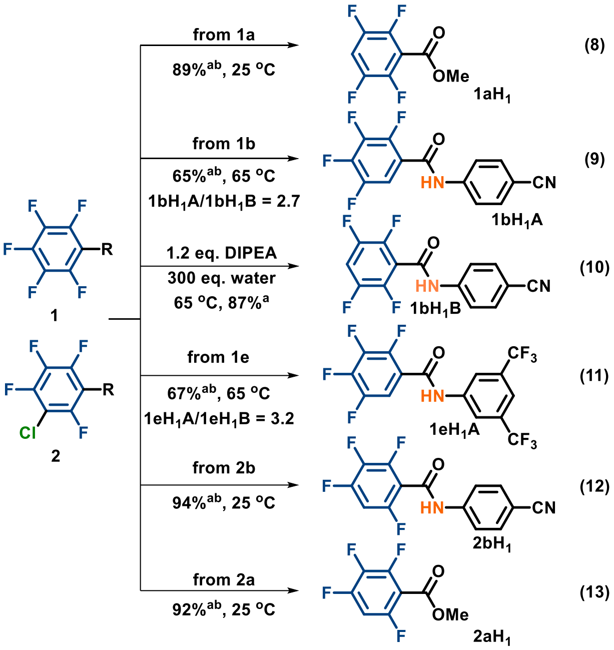
[a]Reaction conditions: Same as in eqn 1. [b]Ratio of regioisomers based on crude 19F NMR.

Thus, by simply controlling the moisture content, the equivalents of DIPEA, reaction temperature, and reaction time, we were able to access 5 different fluorinated congeners in good to excellent yields from a single fluorinated core.

We next sought to systematically develop routes to access other multifluorinated patterns. We began by laying out a clear strategy to enumerate the different tetra-fluorobenzoates (**Scheme 4**). First, if the 4-H product was desired, the most straightforward route was the photo-HDF of commercially available benzoate methyl ester (89%, eqn 8), though as mentioned the amide under wet conditions will also yield the 4-H product (eqn 10). Equation 9 and 11 demonstrate the directed-HDF strategy to obtain the ortho-H amide as the major product. The meta-H benzoate was obtained by starting with meta-Cl benzoate or amide (eqn 12, 94%, eqn 13, 92%). This relies on the halogen control which is observed when there is a heavier halogen atom on the same ring- despite its position on the ring. Thus, halogen control outcompetes both electronic- and directed-HDF.[10a] Thus, from 2 cores all potential mono-H motifs can be obtained.

We turned our attention towards obtaining the di-hydrofluoro benzoates (**Scheme 5**). The difference in rate constants for

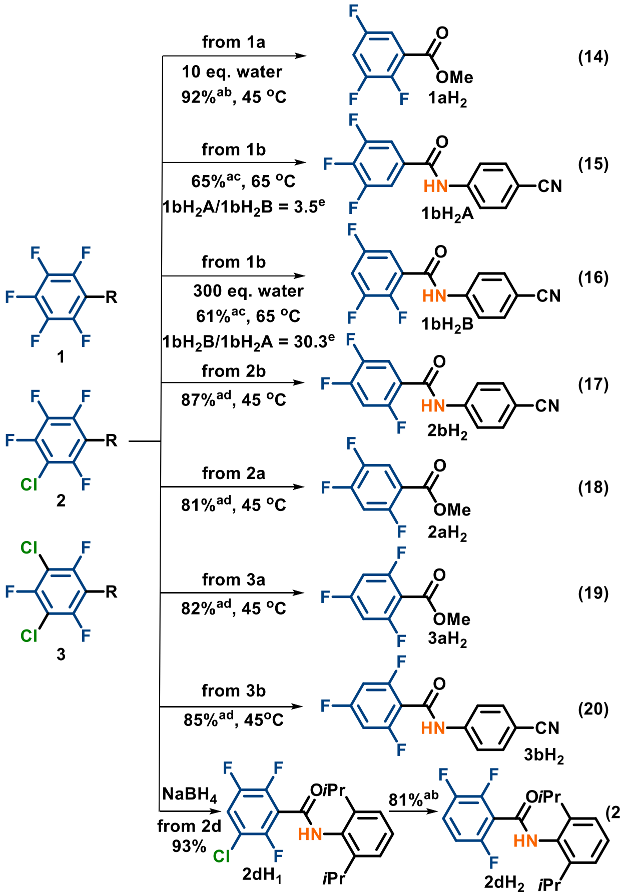
Scheme 4. Exploring the tetrafluorinated benzoyl motifs



[a]Reaction conditions: Same as in eqn 1 except, DIPEA (1.2 equiv).
[b]Isolated yield for $1bH_1A$ as only product.

mono- and di-reduction is significant, and selectivity can be achieved by varying the equivalents of amine and the reaction temperature, along with careful monitoring of reaction progress. The di-H product obtained under electronic control is the 2,4 di-H product which was obtained starting with the methyl benzoate (eqn 14). Again, using the amide **$1bH_0$** under dry conditions (eqn 15) we were able to mostly shut down electronic HDF and instead obtain 2,6-di-HDF as the product **$1bH_2A$** in a good yield (65%) and good selectivity (3.5 rr). In contrast, the 2,4-di-HDF product could be obtained by intentionally adding water to the reaction (eqn 16), with excellent selectivity. Typically, the easiest way to obtain a meta-H was to utilize halogen control strategy using starting material derived from commercially available 3-chlorotetrafluorobenzoic acid. Coupling halogen control with photo-d-HDF (eqn 17, eqn 18) we obtained the 2,5 di-H products (**$2bH_2$, $2aH_2$**) in excellent yields (87%, 81%). Importantly, the first dehalogenation directs the second event to occur para to the first, i.e., neither 2,3-, 3,5- nor the 3,4-defluorinated products are observed. If 3,5-motifs are desired, then halogen controlled di-dechlorination of **$3aH_0$** and **$3bH_0$** (eqn 19, eqn 20) provide **$3aH_2$** and **$3bH_2$** in excellent yields (82%, 85%). The 3,4-defluorinated motif can be obtained by first employing borohydride based HDF[24] conditions developed earlier by our group,[24] followed by the photo-HDCl (photocatalytic hydrodechlorination) to yield **$2dH_2$** in 75% overall yield (eqn 21). While the S_NAr based- and photocatalytic-HDF selectivity often coincide, their selectivity diverges when heavier atoms are involved. Similar experiments with the ester failed and were plagued by carbonyl chemistry.[25] In total, this allows access to four different di-H benzoyl motifs, one pattern of which is a medicinally relevant organofluorine used in the synthesis of Januvia.[1c]

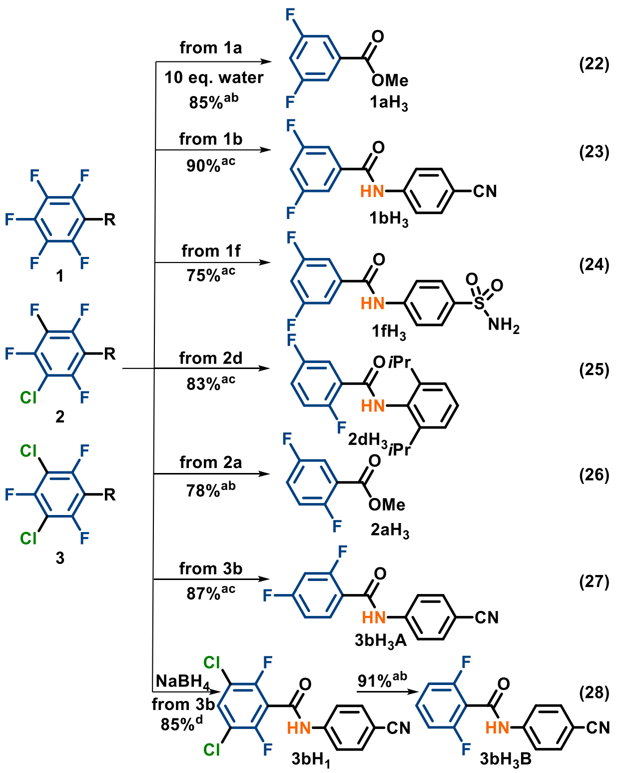
Scheme 5. Exploring the trifluorinated benzoyl motifs



^{a}Reaction conditions: Same as eqn 1 but DIPEA ^{b}(1.2 equiv), ^{c}(2.2 equiv), ^{d}(5.0 equiv). ^{e}Ratio of regioisomers based on crude 19F NMR.

We next investigated the tri-HDF series (**Scheme 6**). Again, the degree of hydrodehalogenation, i.e., di- versus tri-HDF, can often be controlled by the equivalents of amine, and the reaction temperature. For example, while di-HDF of **1aH$_0$** gives **1aH$_2$** in excellent yield (eqn14, **Scheme 5**), increasing the loading of DIPEA from 1.2 to 5 equivalents, increasing the temperature from 45 ºC to 65 ºC, and extending the reaction time from 12 to 24 h, allows the tri-HDF of substrate **1bH$_0$** to give **1bH$_3$** in excellent yield, 85% (eqn 22, **Scheme 6**). Despite a different reaction path, the same pattern emerged with both our standard *p*-cyanophenyl amide (**b**, eqn 23) as well as the pharmaceutically relevant *para*-sulfonamide motif (**f**, eqn 24). They were isolated in excellent to good yields. Next, we sought to access the 2,4,5-tri-H pattern by use of halogen control followed by ortho and a para di-photo-HDF on an amide derived from 2,6-di-isopropyl aniline (eqn 25, **Scheme 6**). The amide was chosen because we anticipated that it would prefer HDF at the 4-position based on its preference for 4-HDF observed early on in our studies (**Fig. 2**). Indeed, this resulted in a 3,6-difluorobenzoyl motif (**2dH$_3$**) being isolated in good yield (83%). Experiments with the benzoate (eqn 26) also gave the same product and suggested that this was the electronic product. Taking advantage of the para-cyano amide's directing ability, the 3,5-dichloro (**3**) motif was used with halogen control to expose both *meta*-Hs and then photo-d-HDF to remove an *ortho*-fluorine to obtain **3bH$_3$A** in excellent yield (87%, eqn 27). This approach allows access to few different fluorination patterns which are challenging to access and yet are found in several important molecules such as teflubenzuron,[26] omarigliptin,[27] dolutegravir,[27a,28] dabrafenib,[27a,29] cobimetinib,[27a] and diflunisal.[30] Next, we turned our attention towards obtaining the *2,6*-di-fluorobenzoate derivative (**3bH$_3$B**, eqn 28). Attempts to obtain this compound using the dichloromethyl benzoate (**3a**) were unsuccessful. While photo-HDCl

Scheme 6. Exploring the difluorinated benzoyl motifs

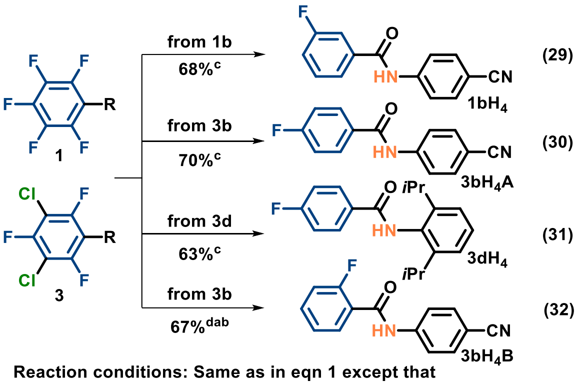


^{a}Reaction conditions: Same as in eqn 1, except DIPEA. ^{b}(5.0 equiv), ^{c}(8.0 equiv), 65 °C. ^{d}NaBH$_4$ (1 equiv) , DMSO, rt.

occurred rapidly, further HDF was not feasible. Extended reaction times and in the presence of water only led to slow hydrolysis of the intermediate. While use of the amide did lead to further directed-HDF, we were still not able to achieve the 3,4,5-tri-H pattern. We successfully achieved this pattern by first use of NaBH$_4$ in DMSO[24] which selectively gave HDF via nucleophilic aromatic substitution to give **3bH$_1$** in high yield (85%). Subsequent addition of 5 equivalents of DIPEA to **3bH$_1$** at 65 ºC with irradiation resulted in the di-photo-HDCl to give **3bH$_3$B** in two-steps with a combined 77% yield (eqn 28).

We next investigated the routes to generate the monofluorinated isomers through selective HDF (**Scheme 7**). Admittedly, the molecular sculpting approach is less attractive when an arene contains only a single fluorine, especially in the case of a simple benzoate. However, we believe that this systematic study may be informative in the case of more structurally complex fluorinated molecules. Thus, we asked which, if any, of the monofluorobenzoyl motifs we could obtain. We found that the *meta*-F benzoate could be synthesized by starting with the amide (**1bH$_0$**) which we found underwent ortho-, ortho-, para-, and finally meta-defluorination under prolonged reaction times to provide access to mono-fluorinated derivative **1bH$_4$** (enq 29) in good yield (68%). The key to reaction was increasing the reaction temperature, DIPEA loading, and lengthening the reaction time. Access to the *para*-fluoro motif was achieved by starting with the reaction of amide **$3bH_0$** (eqn 30) and exploiting halogen control to first remove the meta-chlorines, followed by di-photo-d-HDF to remove the ortho fluorines to give **$3bH_4A$** in 70% yield. The same strategy could be employed using the much bulkier (**3d**, eqn 31) amide which is also an effective directing group to yield **$3dH_4$** in similar yield (63%). This result, might seem surprising, given the previously observed preference for 4-HDF by this group (Fig 2), but can be rationalized by first dechlorination which directs the next HDF event to occur para to the first installment of hydrogen.[31] Finally, to complete the sequence, we needed to develop a strategy to obtain the *ortho*-F product. We were able to achieve this using the previously described S_NAr-HDF, followed by di-photo-HDCl, followed by photo-d-HDF to remove one of two remaining fluorines to yield **$3bH_4B$** in 67% (eqn 32). While this would be a moderate yield for a single- step transformation, it is remarkable considering that two chlorines and two fluorines were selectively substituted in this transformation. Finally, to complete our study, we turned our attention towards obtaining the desfluorobenzoate (**$3bH_5$**, **Scheme 8**). We anticipated **$3bH_4B$** was key to obtaining this objective. Previously, Tan[32] has shown that *fac*-Ir(ppy)$_3$ when used with tBuOK is capable of defluorinating ortho-fluorinated benzamides to afford an annulated product that presumably proceeds through a similar radical anion intermediate. Hence, by adding 100 equivalents of water which we found necessary, we were able to drive the final HDF and complete hydrodehalogenation in excellent 1-step yield (94%) from **$3bH_4$**, or a 73% 3-step yield starting from **3b**.

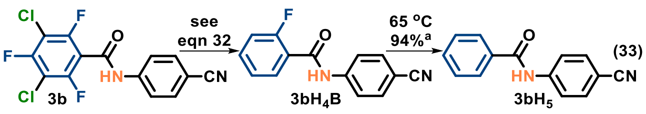
Scheme 7. Exploring the monofluorinated benzoyl motifs



Reaction conditions: Same as in eqn 1 except that DIPEA ^{a}(5.0 equiv), ^{b}(6.0 equiv and 50 equiv water), ^{c}(10.0 equiv), 65 °C. ^{d}NaBH$_4$ (1 equiv), DMSO, rt.

Having provided strategies to rapidly access several fluorinated benzoate congeners, some of which would be difficult to access via traditional methods, we wanted to explore the applicability of our products.

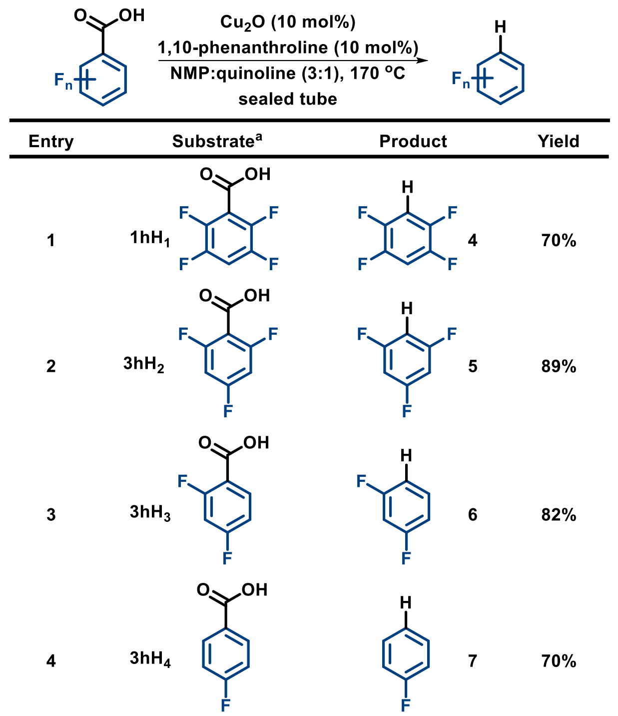
Scheme 8. Exploring the complete dehalogenation



Reaction conditions: Same as eqn 1 but ^{a}DIPEA (8.0 equiv), H$_2$O (100 equiv).

Benzoates, of course, can serve as a precursor for many other functional groups, including a proton, as demonstrated by Goossen[33] and others'[34] copper-catalyzed decarboxylative protonation. Indeed, we found that the copper catalyzed decarboxylative conditions reported by Goossen to be straight forward to use with our benzoate products. Recently, Neufeldt and Topczewski[35] studied the palladium catalyzed decarboxylative cross-coupling of fluorinated benzoates and observed that the presence of ortho fluorines facilitated the decarboxylation step.

Scheme 9. Exploration of decarboxylation of fluorinated benzoic acids

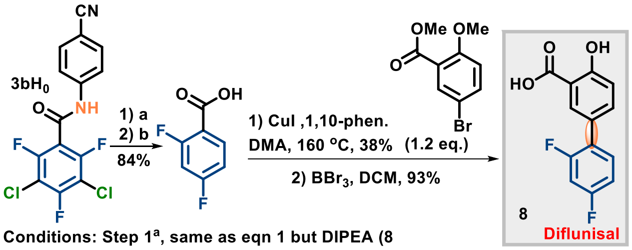


Entry	Substrate^a	Product	Yield
1	$1hH_1$	4	70%
2	$3hH_2$	5	89%
3	$3hH_3$	6	82%
4	$3hH_4$	7	70%

However, under these conditions,[33] we found that decarboxylation occurred rather smoothly regardless of fluorine content, though the kinetics of the reactions were not followed. For example, when carboxylic acid **$3hH_2$** was subjected to Cu$_2$O, and 1,10-phenanthroline in NMP/quinoline (3:1) at 170 °C for 17 hours, 1,3,5-trifluorobenzene was produced (**5**, **Scheme 9**) in excellent yield 89%, while the 4-fluoro substrate (entry 4) resulted in a 70% yield. It should be noted that these reactions were performed in a sealed microwave vial to prevent the loss of the significantly more volatile product. However, in all cases we examined, the acid is readily accessible *via* the acidic hydrolysis of the corresponding defluorinated benzamides and basic hydrolysis of the ester motifs (see SI for details) and all readily underwent decarboxylative protonation.

Next, building further upon Liu's Cu(I) based decarboxylative-cross coupling technology,[36] we attempted to directly synthesize biaryls with aryl halides (**Scheme 10**). First, we established the desired fluorination pattern via photocatalytic dehalogenation, followed by hydrolysis to obtain the difluorinated acid. This acid was directly coupled with brominated methylated methyl salicylate to forge the key C–C bond connecting the two aryl rings found in the commercial anti-inflammatory drug, diflunisal (**8**), which was realized after demethylation.[37] A moderate yield for the coupling step was obtained whereas the demethylation step was high yielding (93%). This scheme illustrates the power of the molecular sculpting approach when combined with other transformations to access important fluorinated molecules.

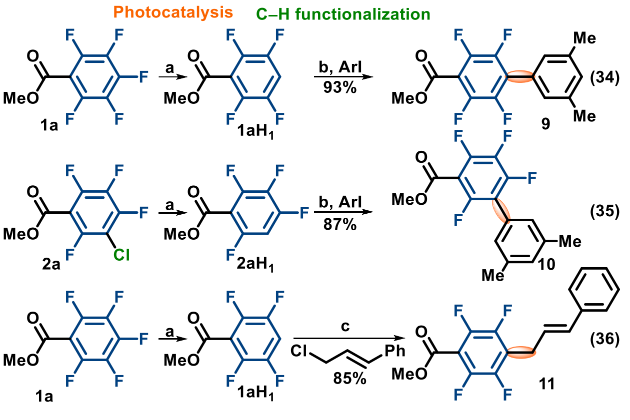
Scheme 10. Tandem molecular sculpting and decarboxylative cross-coupling



Conditions: Step 1[a], same as eqn 1 but DIPEA (8 equiv) at 65 °C. Step 2[b], Reflux 12 M HCl.

In addition to the ability to decarboxylatively cross-couple the benzoate motif, Fagnou,[38] Daugolis,[39] and others[40] have shown that the enhanced acidity of C–Hs (compared to non-fluorinated arenes), such as those found on highly fluorinated arenes, can be exploited for cross-couplings. Thus, we investigated the ability to wed the photocatalytic sculpting technique with C–H functionalization chemistry (**Scheme 11**). After subjecting substrates to photocatalytic dehalogenation, we were able to facilitate the palladium catalyzed C–H functionalizations in good yields. Starting with the HDF product **1aH$_1$**, we were able to obtain the cross-coupled product **9** in excellent yield, 93%. In contrast, the dechlorinated product **2aH$_1$** could be utilized for the formation of the coupled product at the 3-position. Additionally, we demonstrated C–H cinnamylation was feasible.[41] Specifically, the HDF product **1aH$_1$** was treated with cinnamyl chloride Pd-catalyst and cesium carbonate to provide **11** in good yield (eqn 36). Together, these results demonstrate the rational use of molecular sculpting and direct C–H functionalization strategies to rapidly expand accessible organofluorine chemical space. Furthermore, the process can be iterative, further enhancing the utility of this sequence. When the new biaryl compound **9** (eqn 37, **Scheme 12**) was resubjected to photocatalysis, a fluorine ortho to the ester and meta to the aryl group was re moved to form a new trifluorobiaryl, **9a**. Similarly, if biaryl **10** was resubjected to photocatalysis, the 2-fluoro group (ortho to the ester group) was removed to form another trifluorobiaryl, **10a** (eqn 38). This result, along with eqn 18 suggest that the position ortho to the ester is more electronically activated than the para position when there is a meta substituent (aryl or H) directing the HDF, and when present, will preferentially fragment the 2-F. Importantly, this highlights the ability to interweave HDF and C–H coupling followed by another HDF event to afford molecules that would otherwise be synthetically challenging to access.

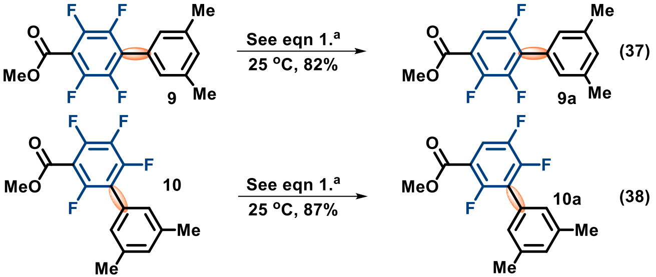
Scheme 11. The merging of halogen sculpting and C–H cross coupling



Reaction conditions: [a]Same as eqn 1. [b]Pd(OAc)$_2$ (5 mol%), PPh$_3$ (10 mol%), Ag$_2$CO$_3$ (0.75 equiv), DMF, 70 °C, ArI = 1-iodo-3,5-dimethylbenzene. [c]Pd(OAc)$_2$ (10 mol%), PivOH (10 mol%), Cs$_2$CO$_3$ (1.5 equiv), toluene, 140 °C.

Often, chemists are faced with the task of creating entirely new synthetic routes to access highly related fluorinated analogs. Thus, we believe our approach is attractive. By applying just a few related strategies from a few commercially reagents, we can expeditiously access many fluorinated analogs. To highlight the relevance of this chemistry we attempted to provide expedited paths to commercially valuable organofluorines.

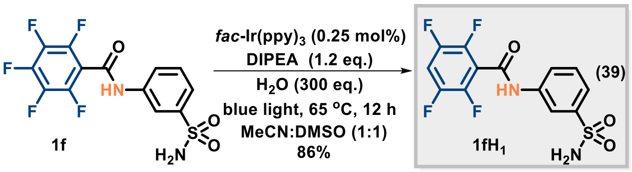
Scheme 12. Iterative HDF and C–H cross coupling



Reaction conditions: [a]*fac*-Ir(ppy)$_3$ (0.25 mol%), MeCN (0.1 M), Ar, blue LEDs, DIPEA (1.2 equiv).

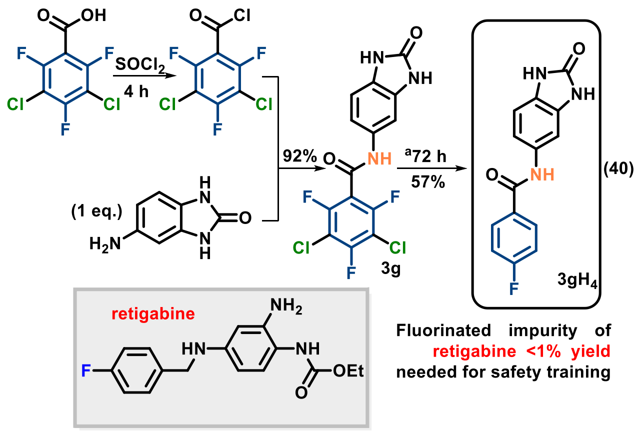
The tetrafluorobenzoyl motif which is found in the carbonic anhydrase inhibitor (**1fH$_1$**, **Scheme 13**), is believed to regulate the intraocular pressure of the eye and has been studied as an antiglaucoma medication that can be used topically.[42] Performing the HDF reaction under wet conditions affords the electronically controlled HDF product **1fH$_1$**. The substrate is only modestly soluble in MeCN but its solubility can be increased substantially when DMSO is added as a cosolvent along with water as an additive, which result in the high yield of the electronically controlled HDF product (eqn 39).

Scheme 13. Synthesis of a carbonic anhydrase inhibitor



While we have demonstrated several examples of how the molecular sculpting approach can provide convenient access to important fluorinated molecules, it is also important to realize that it may also facilitate the study of drugs in other ways. For instance, retigabine was a drug that was marketed as an anticonvulsant,[43] though it has since been removed from the market.[44] In the development of the drug several related organofluorine impurities were produced in low yield (<1.5%, **Scheme 14**). The safety profile of these impurities had to be assessed, as is often the case, and thus, required synthesis. Because the impurities are produced in (hopefully) low quantities *via* the synthetic route to the drug, typically, entirely new routes must be developed, requiring valuable time and effort. Here we demonstrate an efficient synthesis of a fluorinated impurity of retigabine in two steps from commercial material. The impurity contained 4-fluorobenzamide with a cyclic urea, and we hoped that this amide would efficiently undergo the di-photo-d-HDF to yield the desired product after di-photo-HDCl occurred. The starting amide was of moderate solubility in MeCN, so dry DMSO was added to increase solubility. Indeed, this approach provides rapid access to this fluorinated impurity in 57% yield and could expedite access to such impurities.

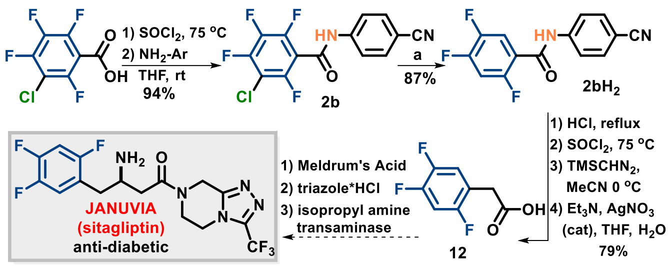
Scheme 14. Synthesis of a retigabine impurity



Reaction condtions: ^{a}Same as eqn 1, except DIPEA (10 equiv), MeCN:DMSO (1:1), and 65 °C.

Januvia is an important anti-diabetic drug marketed by Merck. The trifluorination pattern found in the key acid used in the synthesis of Januvia can be obtained using a combination of halogen control and photo-d-HDF on the amide **1bH$_0$**, followed by homologation of the acid via a Wolff rearrangement (**Scheme 15**). The key intermediate **12** was obtained without the need for chromatography in excellent yield, 79%.[45]

Scheme 15. Synthesis of 12, an intermediate en route to Januvia



Reaction conditions: ^{a}Same as in eqn 1, except DIPEA (5.0 equiv), and 45 °C.

In conclusion, we have investigated the ability to utilize the photo-d-HDF of fluorinated arenes. We have identified and highlighted several control elements available to synthetic chemist that will expedite their efforts to access and explore fluorinated chemical space. We have identified several key factors that control the photo-HDF, they are:

1. Halogen size
2. Substituent electronics (para directing)
3. Substituent H-bonding (directed HDF)

    The disruptive/accelerative effect of water

    The disruptive effect of steric bulk

Namely, we have seen that halogen control will reliably remove the heaviest halogen. Specifically, we have observed that a chlorine will be preferentially fragmented over a fluorine- regardless of its position.[14] Secondary to the halogen control, is the inherent electronic control of substrate, and in the case of an ester and amide group is *para* to the carbonyl group, followed by *ortho*, followed by the other *ortho*. Intramolecular hydrogen bonding from non-bulky amides makes up the tertiary control element and will preferentially undergo directed-HDF at the *ortho* positions. Acidic aryl amides work well, but the phenomenon may extend beyond this motif. In the event that the electronic and the directed product are not the same, the exact regioselectivity will be a function of the acidity of the amide and can range from synthetically useful to excellent. Importantly, the presence of water in the reaction plays an important role of disrupting the hydrogen bond directing effect and can be used to intentionally return the selectivity to the electronically controlled product. We have also seen that the addition of water can be used help accelerate defluorination- in the event that the HDF is sluggish. Additionally, if an amide is bulky, it may also inhibit the hydrogen bond directing effect and result in the electronically controlled product, albeit sluggishly. Finally, we have observed that fluorines flanked by hydrogen are less prone to fragment- which may be a result of the structure of the radical anion, and which is expected to have a significant effect on the rate and regioselectivity of mesolytic fragmentation of fluoride.[46]

We have investigated four complementary techniques for building various useful fluorination patterns, they are:

1. S_NAr HDF
2. decarboxylative coupling
3. decarboxylative protonations
4. C–H functionalizations

Specifically, we have shown how the S_NAr-HDF, while often giving the same selectivity as electronic control, diverges in the presence of heavier halogens. Finally, we also demonstrated how the benzoyl group could first be used to yield the appropriate fluorination pattern, and then subsequently decarboxylated to yield fluorinated benzenes, and fluorinated biaryls. Furthermore, we showed that iterative HDF and C–H functionalization was possible. Given the number of C–Hs that can now be systematically revealed, we anticipate the utility of these two technologies should be synergistically enhanced. Finally, we have applied the defluorination strategies in several different scenarios in hopes of highlighting how it may be used to enhance the access to organofluorine space.

ASSOCIATED CONTENT

- Data Availability Statement
  The data underlying this study are available in the published article and its online supplementary material.
- Supporting Information Statement
  The Supporting Information is available free of charge at http://pubs.acs.org." ^{1}H, ^{13}C, ^{19}F spectra, as well as key 2-D NMR spectra, other characterization, and synthetic procedures (FID). FAIR Data is available as Supporting Information for Publication and includes the primary NMR FID files for compounds: [1aH$_1$, 1aH$_2$, 1aH$_3$, 1bH$_1$A, 1bH$_1$B, 1bH$_2$A, 1bH$_2$B, 1bH$_3$, 1eH$_1$, 1fH$_1$, 1fH$_3$, 1hH$_1$, 2aH$_1$, 2aH$_2$, 2aH$_3$, 2bH$_1$, 2bH$_2$, 2dH$_1$, 2dH$_2$, 2dH$_3$, 3aH$_0$, 3aH$_2$, 3bH$_1$, 3bH$_2$, 3bH$_3$A, 3bH$_3$B, 3bH$_4$A, 3bH$_4$B, 3bH$_5$, 3dH$_0$, 3dH$_4$, 3gH$_0$, 3gH$_4$, 3hH$_2$, 3hH$_3$, 3hH$_4$, 4, 5, 6, 7, 8, 9, 10, 11, 12, 9a, 10a, NMe-1bH$_1$B, 2hH$_2$, 1dH$_0$, 1cH$_0$, 3bH$_0$,

2dH$_0$, 2bH$_0$, 2aH$_0$, NMe-1bH$_0$, 1iH$_0$, 1fH$_0$, 1eH$_0$, 1bH$_0$, and 1bH$_4$].” (zip)

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