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RESEARCH ARTICLE

Directed Palladium Catalyzed C–H (Ethoxycarbonyl)difluoro-methylthiolation Reactions

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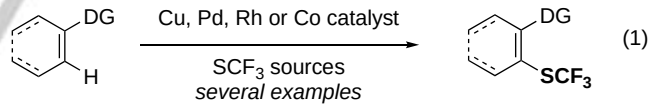
Abstract: The unprecedented Pd-catalyzed (ethoxycarbonyl)difluoromethylthiolation reaction of various unsaturated derivatives was studied. In the presence of the (ethoxycarbonyl)difluoromethylsulfenamide reagent **I** and under mild reaction conditions (60 °C), both 2-(hetero)aryl and 2-(α-aryl-vinyl)pyridine derivatives were smoothly functionalized with this methodology (37 examples, up to 87% yield). Moreover, the synthetic interest of this fluorinated moiety was further showcased by its conversion into various original fluorinated residues. Finally, a plausible mechanism for this transformation was suggested.

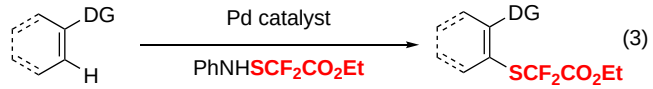
Introduction

In a society fully aware about the next challenges towards greener chemistry and the global welfare, the prevalence of organofluorinated molecules in our daily life should be taken into consideration. Cognizant about their pivotal role in medicinal chemistry programs and material science,[1] the quest for efficient and sustainable routes to novel fluorinated molecules is of prime importance.[2] In that context, the design of fluorinated residues that might be easily converted in various other fluorinated functional groups like a swiss-army knife is of paramount importance. Therefore, over the last years, a strong interest of the scientific community was dedicated to the synthesis of original and functionalized fluorinated moieties such as CF_2R and SCF_2R (R = H, CO_2Et, $PO(OEt)_2$, SO_2Ph…).[3]
Besides, transition metal catalyzed C–H bond activation has completely revolutionized the field of organic chemistry and has become a sustainable tool to reach molecular complexity.[4] Despite significant advances, the formation of C–S bond by C–H bond activation remains an underexplored area.[5] Pursuing our efforts on the development of innovative transformations to forge C–S bond by Pd-catalyzed C–H bond activation,[6] we aimed at tackling the unmet challenge to build up a $C(sp^2)$–SCF_2FG (FG = functional group) by C–H bond activation, with a particular focus on the SCF_2CO_2Et moiety, due to its versatility and the lack of available methods to introduce it on molecules.
So far, such strategy is mostly restricted to the trifluoromethylthiolation reaction (Scheme 1, eq.1.). These reaction manifolds mainly used Cu,[7] Pd,[6b-c],[8] Rh,[9] and Co[10] complexes as catalysts. Of note, a unique report dealing with the difluoromethylthiolation of acrylamides was recently depicted (Scheme 1, eq. 2).[11] In light of the conspicuous absence of methodology to introduce other possible SR_f motifs by C–H bond activation, and particularly functionalized ones, we sought to dedicate efforts to broaden the current portfolio of available transformations. In this context, we disclosed herein the Pd-catalyzed C–H (ethoxycarbonyl)difluoromethylthiolation reaction of $C(sp^2)$ centers (Scheme 1, eq. 3).

State of the art:

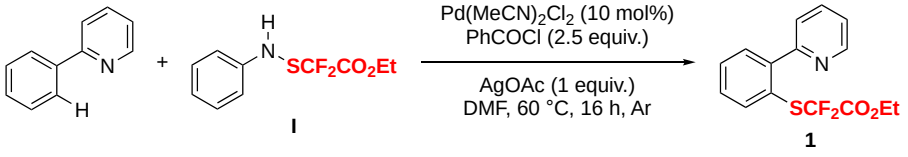


This work:



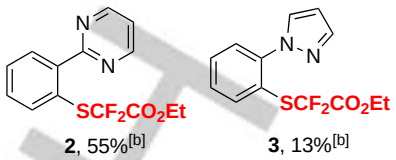
Scheme 1. Introduction of SR_f motifs by C–H bond activation, state of the art and present work.

A. Optimization of the Reaction

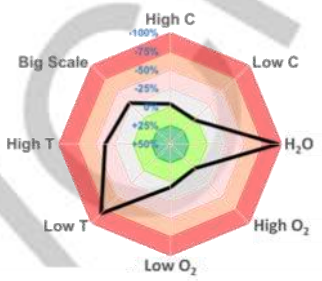


Entry	Variation from the standard conditions	Yield (%)[a]
1	***none***	**74, (74)[b]**
2	no PhCOCl	0
3	$Pd(TFA)_2$, $Pd(OAc)_2$ instead of $Pd(MeCN)_2Cl_2$	<30
4	40 °C instead of 60 °C	26
5	100 °C instead of 60 °C	75
6	toluene, DMSO or 1,4-dioxane instead of DMF	0
7	5 mol% of $Pd(MeCN)_2Cl_2$	40
8	1.2 equiv. of **I** instead of 2.5 equiv.	55

B. Other Suitable Directing Groups



C. Sensitivity Assessment



Scheme 2. A. Optimization of the reaction conditions. B. Other suitable directing groups. C. Assessment of the sensitivity. [a] ^{19}F NMR yields using α,α,α-trifluoroacetophenone as an internal standard. [b] Isolated yields.

Results and Discussion

At the outset of the study, we chose the reagent **I**, previously reported by our group,[12] as the electrophilic source of the SCF_2CO_2Et residue, in combination with a Pd(II) catalyst. After an extensive set of optimization reactions, we found that pyridine was the most efficient directing group in this transformation (Scheme 2A).[13] Indeed, the corresponding product **1** was isolated in 74% yield, using 10 mol% of $Pd(MeCN)_2Cl_2$, one equivalent of AgOAc as an additive in DMF under mild reaction conditions (60 °C) for 16 h (Scheme 2A, entry 1). Importantly, the addition of 2.5 equivalents of PhCOCl as an additive to activate the reagent **I**, as disclosed by Liu, was crucial to ensure the reaction (Scheme 2A, entry 2).[8b] It is worth mentioning that $Pd(MeCN)_2Cl_2$ was the most efficient catalyst (Scheme 2A, entry 3). Lower reaction temperature was detrimental to the reaction, while the use of higher reaction temperature did not improve the reaction efficiency (Scheme 2A, entries 4 and 5). The nature of the solvent was important and DMF remained the most efficient one (Scheme 2A, entry 6). Finally, a decrease in catalyst loading or the amount of the reagent **I** provided **1** in lower yields (entries 7 and 8). Note that among the other tested directing groups,[13] two *N*-heterocycles were suitable as the directing group, although the yields were lower (Scheme 2B). To highlight the versatility and the reproducibility of our reaction conditions, the sensitivity assessment with regard to the reaction parameters was achieved.[14] This transformation was insensitive to an increase of the reaction temperature, the scale of the reaction, the presence of oxygen and the concentration. However, the yields dropped significantly when the reaction was carried out at low temperature or in the presence of H_2O.

Then, having delineated the optimal reaction conditions, the scope of this methodology for the introduction of the SCF_2CO_2Et residue by C–H bond activation was evaluated (Scheme 3). First, we successfully scaled up the reaction to a 3 mmol scale, and **1** was isolated in 50% yield. Pleasingly, the reaction was extended to the functionalization of the benzo[*h*]quinoline, giving the corresponding SCF_2CO_2Et-containing molecule **4** in 80% yield. The replacement of the phenyl ring by a naphthyl ring did not affect the reaction outcome, since the 2-(2-naphthyl)-pyridine was successfully functionalized in 87% yield with a complete selectivity for the C–3 position of the naphthalene residue. The introduction of an electron-donating substituent at the *para*-position of the phenyl residue was well-tolerated. Indeed, methyl, phenyl, methoxy, a *N*-Boc-protected amine as well as an acetal group were compatible, affording the desired products **6**-**10** in good to high yields. Halogen atoms (bromide, chloride and fluoride) were not altered during the reaction, offering possibilities for further orthogonal C–C or C–N bond formation, for instance. The introduction of electron-withdrawing groups, like trifluoromethyl, aldehyde, ester, cyano, as well as a nitro group did not affect the efficiency of the reaction and the desired SCF_2CO_2Et-containing products **14**-**18** were obtained in moderate to good yields (36% to 70%). Interestingly, the SCF_2CO_2Et product **19**, bearing a OCF_3 substituent, an important motif in drug discovery programs,[15] was isolated in 55% yield. Then, we evaluated the effect of the substitution pattern on the outcome of the reaction. The introduction of a methyl or a cyano substituent at the *meta* position of the phenyl ring did not impact the reaction and the products **20** and **21** were isolated in 63% and 47% yields, respectively. Then, the 2-(2-fluorophenyl)-pyridine was functionalized in 61% yield into the product **22**. Moreover, polysubstituted 2-phenyl pyridines **23** and **24** were readily obtained in 39% and 72% yields, respectively. Finally, the thiophene derivative **25** was obtained in 65% yield, showcasing the possibility to functionalize a heteroaromatic derivative. Then, to further broaden the versatility of our method, we conjectured that our reaction manifold could be extended to the functionalization of 2-vinyl pyridine derivatives. Indeed, such pyridine derivatives highlight a similar reactivity as the aryl-substituted congeners.[16] Moreover, such appealing extension would offer a privileged access to di-, tri- and tetra-substituted SCF_2CO_2Et-containing alkenes in a stereoselective fashion.

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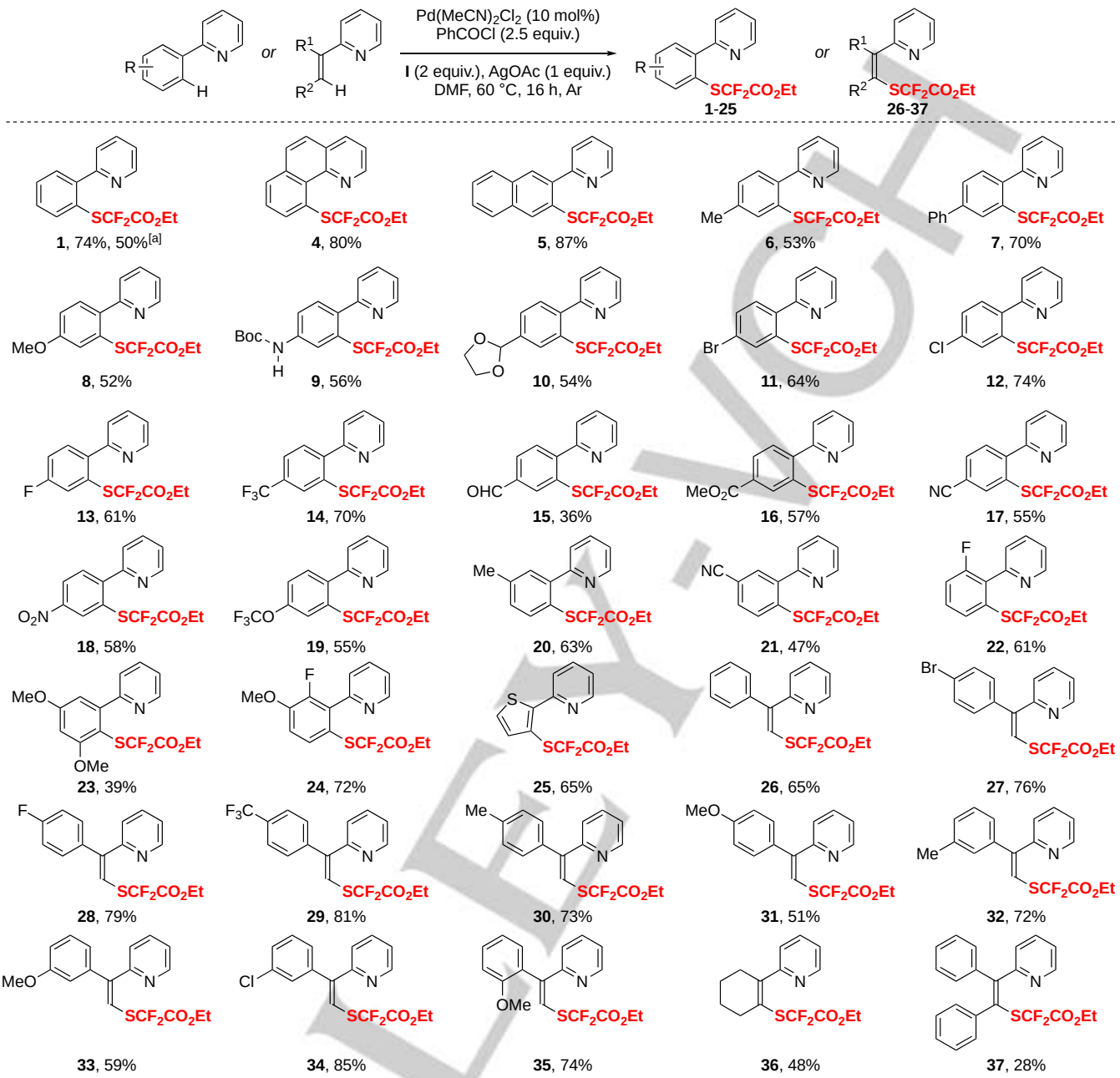
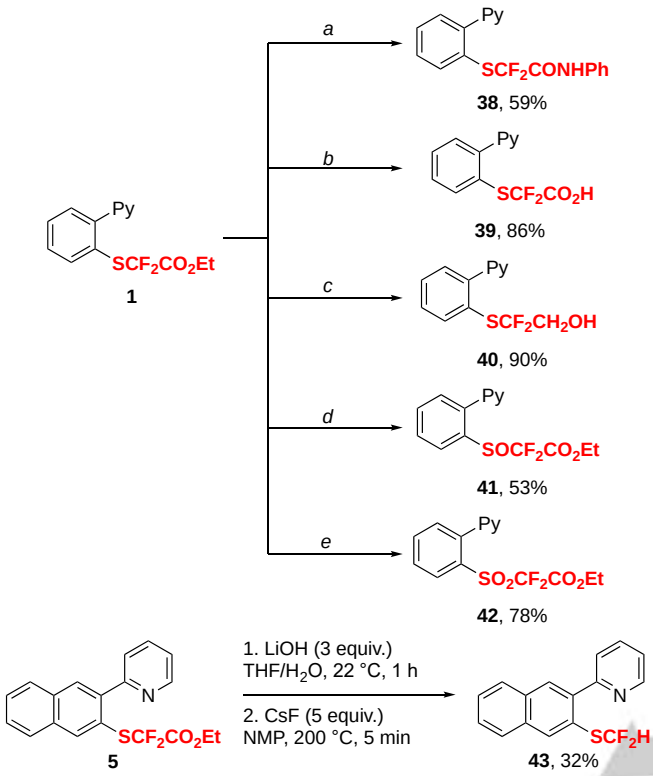


Scheme 3. Evaluation of the scope of the transformation. Reactions were carried out on a 0.3 mmol scale, isolated yields were given. [a] Reaction was carried out on a 3 mmol scale.

To our delight, our reaction conditions allowed the straightforward introduction of the SCF_2CO_2Et motif on the 2-(α-phenyl-vinyl)-pyridine and the alkene **26** was isolated in a 65% yield as a single diastereoisomer *Z*, according to 2D NMR analysis.[13] Then, we extended this process to the functionalization of other 2-aryl-vinyl-pyridine derivatives. The presence of halogen atoms (*i.e.* bromide and fluoride) as well as a trifluoromethyl group at the *para* position of the phenyl ring was compatible, giving the products **27**-**29** in very good yields. Likewise, the substrates having an electron-donating group at the *para* position (**30**-**31**) were smoothly functionalized. The substitution pattern on the aromatic ring did not affect the reaction efficiency, SCF_2CO_2Et-containing derivatives having a *meta* and even *ortho*-substituent on the aryl residue were isolated in good to excellent yields (**32**-**35**, 59% to 85% yield).

Finally, the reaction conditions were suitable for the stereoselective synthesis of the tetra-substituted olefins **36** and **37** in 48% and 28% yields, respectively. Then, to highlight the synthetic interest of the products and the versatility of the SCF_2CO_2Et residue, some key transformations were carried out (Scheme 4). First, the ester residue was readily converted into the corresponding amide **38** in 59% yield, likewise the formation of the acid **39** was performed in an excellent 86% yield. Then, the

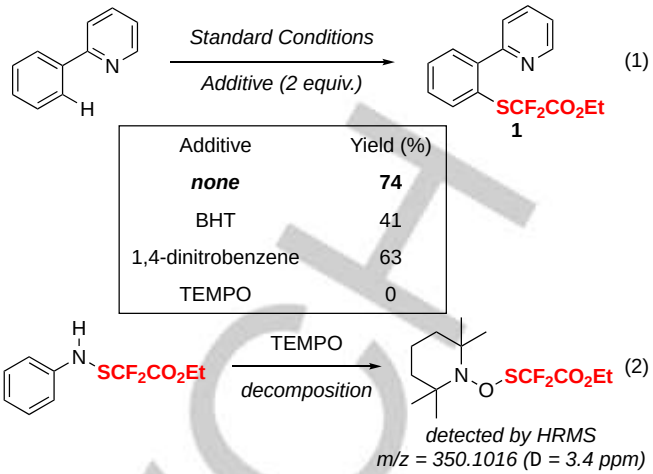
synthetically useful alcohol **40** was obtained in 90% yield upon the reduction of **1** with $LiAlH_4$.



Scheme 4. Synthetic utility of the products. *a)* $PhNH_2$ (1.2 equiv.), *t*-BuOK (2 equiv.), THF, 22 °C, 1 h, Ar. *b)* LiOH (3 equiv.), THF/H_2O, 22 °C, 1 h. *c)* $LiAlH_4$ (1.5 equiv.), THF, 0 °C, 10 min, Ar. *d)* *m*-CPBA (1.2 equiv.), DCM, -15 °C, 2 h, Ar. *e)* H_5IO_6 (4 equiv.), $K_2Cr_2O_7$ (8 mol%), MeCN, 22 °C, 2 h, Ar. Py = 2-pyridyl.

Finally, we have been able to selectively convert the SCF_2CO_2Et group into the corresponding sulfoxide **41** in 53% yield using *m*-CPBA, while the use of H_5IO_6 in the presence of a catalytic amount of $K_2Cr_2O_7$ allowed the formation of the corresponding sulfone **42** in 78% yield. These last transformations offered an unprecedented access to novel fluorinated motifs. Finally, we showcased the conversion of the SCF_2CO_2Et group into the important SCF_2H motif (product **43**), according to a saponification/decarboxylation sequence in an overall yield of 32%.

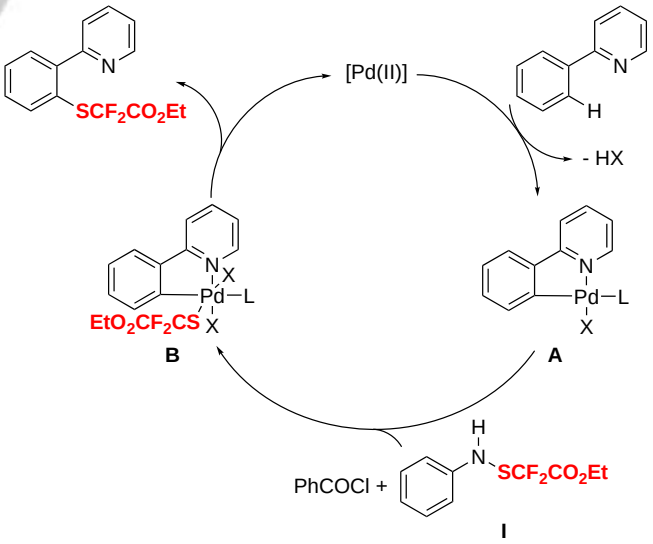
Then, to gain insights into the reaction mechanism, control experiments were carried out (Scheme 5).



Scheme 5. Control experiments. Isolated yields were given.

To preclude a radical pathway, the addition of various additives as radical scavengers or inhibitors was performed (Scheme 5, eq. 1). In the presence of BHT (butylhydroxytoluene) or 1,4-dinitrobenzene, the reactions proceeded, albeit with a slight decrease of the reaction yield. In the presence of TEMPO (2,2,6,6-tetramethylpiperidin-1-yl)oxyl), the reaction was shut down and no product was observed. A complementary experiment (Scheme 5, eq. 2) showcased that the reagent **I** decomposed in the presence of TEMPO, thus explaining the inhibition of the reaction in the presence of TEMPO. Indeed, the TEMPO-SCF_2CO_2Et adduct was detected by HRMS analysis of the crude reaction mixture. Hence, with these data in hand, a free radical pathway might be excluded.

Therefore, according to our observations and along with the literature reports,[17] we suggested the following plausible mechanism for this transformation (Scheme 6).



Scheme 6. Suggested mechanism for the Pd-catalyzed (ethoxycarbonyl)-difluoromethylthiolation reaction.

First, the [Pd(II)] catalyst would react with the 2-phenylpyridine derivative to form the palladacycle **A**. A subsequent oxidative

addition with the reagent **I**, activated with PhCOCl,[8a] would provide the high valent Pd(IV) species **B**, which upon reductive elimination would afford the desired product and regenerate the [Pd(II)] catalyst.

Conclusion

In summary, we disclosed the unprecendeted direct C(sp^2)–SCF_2CO_2Et bond formation by transition metal catalyzed C–H bond activation under mild reaction conditions. This novel transformation allowed the successful synthesis of a large panel of aromatic and olefinic derivatives bearing this emergent fluorinated motif. The versatility of the products was demonstrated through post-functionalization reactions. Finally, a plausible mechanism for this transformation was suggested. We believe that this study will open new perspectives to access unprecedented fluorinated molecules by building up C–SCF_2FG (FG = functional group) bond by C–H bond activation, which were so far restricted to the introduction of the SCF_3 and SCF_2H groups.

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Keywords Organofluorine chemistry • synthetic method • palladium • C–H activation • emerging fluorinated group

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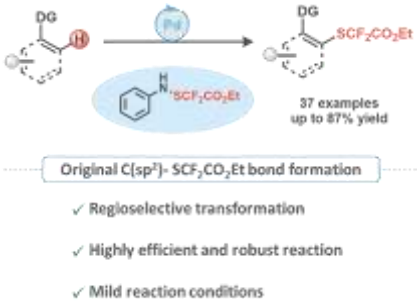

The unprecedented construction of a C(sp^2)-SCF_2CO_2Et bond was successfully achieved by Pd-catalyzed C-H bond activation. This robust protocol allowed the functionalization of a broad panel of aromatic and olefinic derivatives (37 examples, up to 87% yield), a real advance as existing routes were restricted to the SCF_3 and SCF_2H residues. Post-functionalization reactions further illustrated the synthetic value of this fluorinated motif.

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