Synthesis of α-Difluoromethyl Aryl Ketones through a Photoredox Difluoromethylation of Enol Silanes

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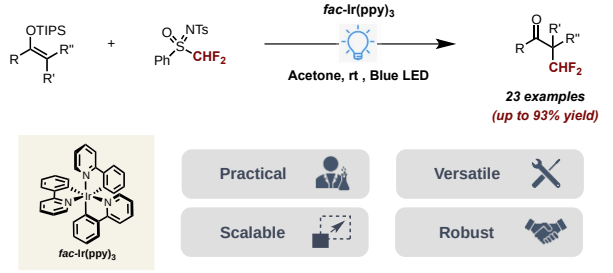
Supporting Information

ABSTRACT: We report here an efficient and highly straightforward access to α-difluoromethylated ketones through a visible light-mediated difluoromethylation of readily available enol silanes. The method, which takes advantage of the polyvalence of Hu's reagent, *N*-tosyl-*S*-difluoromethyl-*S*-phenylsulfoximine, used here as a CHF_2 radical precursor under catalytic photoredox conditions, is practical, scalable, and provides the corresponding α-CHF_2 ketones in good to excellent yields.



The incorporation of fluorine atoms in drugs has been shown to often improve their metabolic stability, enhance their lipophilicity, and increase their membrane permeability and bioavailability.[1] This observation has thus triggered a broad body of work focused on the development of new synthetic methods allowing a straightforward access to fluorinated drug analogues mainly through fluorination[2] and trifluoromethylation processes.[3] The difluoromethyl group has recently attracted a revival of interest due to its ability to act as a weak hydrogen bond donor often compared to carbinols, thiols, amides and hydroxamic acids.[4] It is therefore not surprising that the CHF_2 motif has become prevalent in many pharmaceuticals and agrochemicals.[5] Nonetheless, unlike the fluorination and trifluoro-methylation reactions, which have been widely explored over the years, examples of efficient and reliable difluoro-methylations are more sparse,[6] particularly for the synthesis of α-difluoromethylated ketones.

Traditionally, difluoromethylated compounds are prepared using direct or indirect strategies through electrophilic,[7] nucleophilic,[8] or radical[9] processes. Several effective difluoromethylating agents have been reported over the years such as the tosylsulfoximine **I** developed by Hu and co-workers,[10] the sulfonium and sulfoxinium salts **II** and **III** developed by Shibata,[11,12] the sulfonium salts **IV** and **V** developed by Shen[13] and Liu,[14] respectively, and $TMSCHF_2$ (**VI**), first reported by Hu (Figure 1),[15] which have been successfully used on a variety of aromatic and heteroaromatic scaffolds. However, as mentioned previously, despite the various strategies that have been unveiled, the synthesis of α-difluoromethyl ketones has been much less explored and remains an important synthetic challenge.

In 2012, Mikami and co-workers developed a direct α-difluoromethylation of lithium enolates using fluoroform as an electrophilic difluoromethylating agent (Figure 1. **A**).[16] Although only one example of α-CHF_2-substituted ketone was described with a rather moderate yield of 36%, this was the first example ever reported in the literature.

A few years later, Paquin and co-workers reported a highly regioselective gold-catalyzed formal hydration of propargylic *gem*-difluorides affording a series of 3,3-difluoroketones in high yields, including two examples of α-CHF_2-substituted ketones (Figure 1. **B**).[17] The method took advantage of the strong electron-withdrawing character of the fluorine atoms to direct the selectivity towards the desired carbonyl moiety.

More recently, Akita and co-workers reported a practical and more general approach to α-CHF_2-substituted ketones through a catalytic photoredox keto-difluoromethylation of aromatic alkenes (Figure 1. **C**).[18] The method was applicable to a variety of aromatic and heteroaromatic alkenes and could be scaled up under continuous flow conditions.

Finally, Wang, Wu and co-workers just reported a visible-light-promoted radical difluoromethylation of enol acetates using $[Ph_3PCF_2H]^+Br^-$ as a CHF_2 radical precursor (Figure 1, **D**) affording the corresponding α-CHF_2-substituted aryl ketones in moderate to good yields after 36 h.[19]

Our group has also been involved in the development of new strategies towards the synthesis of difluoromethylated compounds. In this context, we recently reported a general method for the synthesis of CHF_2-containing lactones, lactams, glutaramides, succinimides, quinolinones and Weinreb amides *via* a sequential *C*-selective electrophilic difluoromethylation/palladium-catalyzed decarboxylative protonation.[20] The method, which proved particularly effective, relied on the use of *N*-tosyl-*S*-difluoromethyl-*S*-phenylsulfoximine **I** as a difluorocarbene precursor. Interestingly, this reagent can also be used as a radical CHF_2 source when subjected to catalytic photoredox conditions as showcased by Akita and co-workers.[18,21] This prompted us to explore a new route towards α-CHF_2-substituted ketones through a key photochemical radical difluoromethylation of

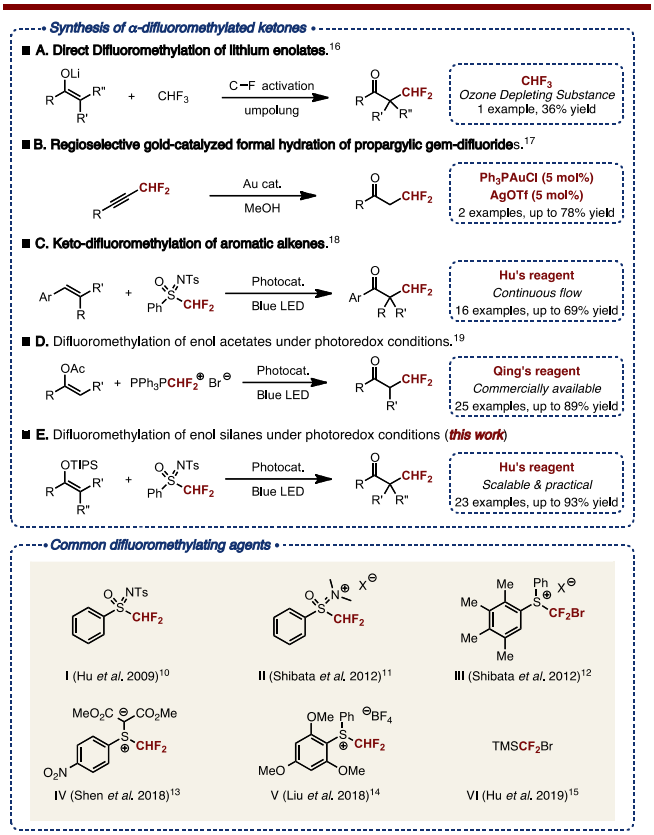
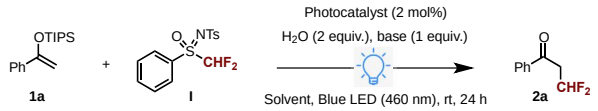


Figure 1. Strategies for the synthesis of α-difluoromethyl ketones.

readily available enol silanes, which is very complementary to Wang and Wu's method (Figure 1. **E**). We report here the results of our endeavor.

To evaluate the feasibility of this photocatalytic difluoromethylation, we chose enol silane **1a** as a model substrate.[22] The latter was prepared in one step and 92% yield starting from commercially available acetophenone (see SI for more details). In our initial screening, we evaluated two common metal-based photocatalysts, namely $Ru(bpy)_3.6H_2O$ (entry 1) and *fac*-$Ir(ppy)_3$ (entry 2), as well as an organic photocatalyst, Eosin Y (entry 3). The reactions were run in acetone at rt for 24 h under visible light irradiation (8 W Blue LED, 460 nm) using a 2 mol% catalyst loading, 1.5 equiv. of Hu's reagent **I** and 2 equiv. of H_2O. Interestingly, only *fac*-$Ir(ppy)_3$ provided the desired α-difluoromethylated product **2a** (77%), which was not surprising considering the higher reduction power (E^*_{ox}) of *fac*-$Ir(ppy)_3$ in its photoexcited state (−2.19 V *vs* SCE)[23] over all the other photocatalysts, allowing it to reduce the difluoromethylated sulfoximine **I** (−2.26 V *vs* Cp_2Fe in DMSO)[18] to the corresponding CHF_2 radical. With this result in hand, we also screened various bases as we believed they could potentially help promote the desilylation step, however the use of DABCO (entry 4) completely inhibited the reaction, while the use of Na_2CO_3 (entry 5) and quinoline (entry 6) decreased considerably the overall yield. The best results were obtained with 2,6-di-*tert*-butylpyridine (2,6-DTP) (entry 7), which afforded the desired α-difluoromethylated product **2a** in an improved 85% yield. Several solvents such as MeCN, DMSO, DMF and toluene were also evaluated under otherwise identical conditions (entries 8-11), but the best solvent remained acetone. Ultimately, increasing the amount of the CHF_2 radical precursor to 2 equiv. led to the best outcome with up to 93%

Table 1. Systematic study.[a]



Entry	Photocatalyst	I (equiv.)	Solvent	Base	Yield[b]
1	$[Ru(bpy)_3]Cl_2 \cdot 6H_2O$	1.5	Acetone	–	0%
2	*fac*-$Ir(ppy)_3$	1.5	Acetone	–	77%
3	Eosin Y	1.5	Acetone	–	0%
4	*fac*-$Ir(ppy)_3$	1.5	Acetone	DABCO	0%
5	*fac*-$Ir(ppy)_3$	1.5	Acetone	Na_2CO_3	22%
6	*fac*-$Ir(ppy)_3$	1.5	Acetone	Quinoline	55%
7	*fac*-$Ir(ppy)_3$	1.5	Acetone	2,6-DTP	85%
8	*fac*-$Ir(ppy)_3$	1.5	MeCN	2,6-DTP	45%
9	*fac*-$Ir(ppy)_3$	1.5	DMSO	2,6-DTP	50%
10	*fac*-$Ir(ppy)_3$	1.5	DMF	2,6-DTP	75%
11	*fac*-$Ir(ppy)_3$	1.5	Toluene	2,6-DTP	21%
12	*fac*-$Ir(ppy)_3$	2	Acetone	2,6-DTP	93%
13[c]	*fac*-$Ir(ppy)_3$	2	Acetone	2,6-DTP	0%
14	–	2	Acetone	2,6-DTP	0%

[a] **Reaction conditions: 1** (0.1 mmol, 1 equiv.), **I** (0.2 mmol, 2 equiv.), photocatalys (0.002 mmol, 2 mol%), base (0.1 mmol, 1 equiv.), H_2O (0.2 mmol, 1 equiv.), solvent (1 mL), rt, 24 h under an argon atmosphere, 8 W blue LED (460 nm). [b] NMR yield determined using benzotrifluoride as an internal standard. [c] Reaction run in the absence of light. [2,6-DTP = 2,6-di-*tert*-butylpyridine, DABCO = 1,4-diazabicyclo[2.2.2]octane].

yield (entry 12) and, most importantly, complete recovery of the additional equivalent of **I**, thus pointing out its role in the catalytic cycle. It is worth mentioning that in the absence of *fac*-$Ir(ppy)_3$ or when running the reactions in the dark, all of the starting material was recovered intact (entries 13-14) while varying the amount of H_2O didn't improve the yield (results not shown, see SI for more details).

After having identified the best set of reaction conditions, we next examined the substrate scope by evaluating a series of silyl enol ethers (Figure 2, **A**).

The reaction appeared to be tolerant to substrates bearing electron-donating groups on the aromatic ring independently of their position. Hence, the *ortho*- (**2b**, 52%), *meta*- (**2c**, 48%) and *para*-methyl-substituted (**2d**, 54%) derivatives as well as the *para*-*tert*-butyl- (**2e**, 62%) and the *para*-methoxy derivatives (**2f**, 64%) were all obtained in decent yields. The reaction appeared to be equally tolerant to substrates bearing electron-withdrawing groups on the aromatic ring such as the *ortho*- (**2g**, 49%), *meta*- (**2h**, 54%) and *para*-bromo-substituted (**2i**, 63%) derivatives, as well as the *para*-chloro- (**2j**, 72%), the *para*-fluoro- (**2k**, 75%), the *para*-trifluoromethyl- (**2l**, 76%) and the *para*-cyano derivatives (**2m**, 51%), which were also obtained in good yields. The method was also used to prepare the 2-naphthyl derivative **2n** (44%) as well as the tertiary α-difluoromethyl ketones **2o** (52%) and **2p** (68%). Quaternary α-difluoromethyl ketones proved much more difficult to obtain as showcased by the low yields obtained for **2q** (15%) and **2r** (13%) after running the reaction over 72 h instead of 24 h.[24] Nonetheless, the reaction was successfully applied to heteroaromatic precursors such as the *N*-methyl imidazole- (**2s**, 62%), the *N*-benzyl pyrazole- (**2t**, 50%), the benzothiophene- (**2u**, 60%) and the 2-furan-derivatives (**2v**, 44% yield), as well as vinyl ketones such as **2u** (46% yield), with the latter process being completely chemoselective. Unfortunately, the method could not be applied to alkyl ketones (**2x**).

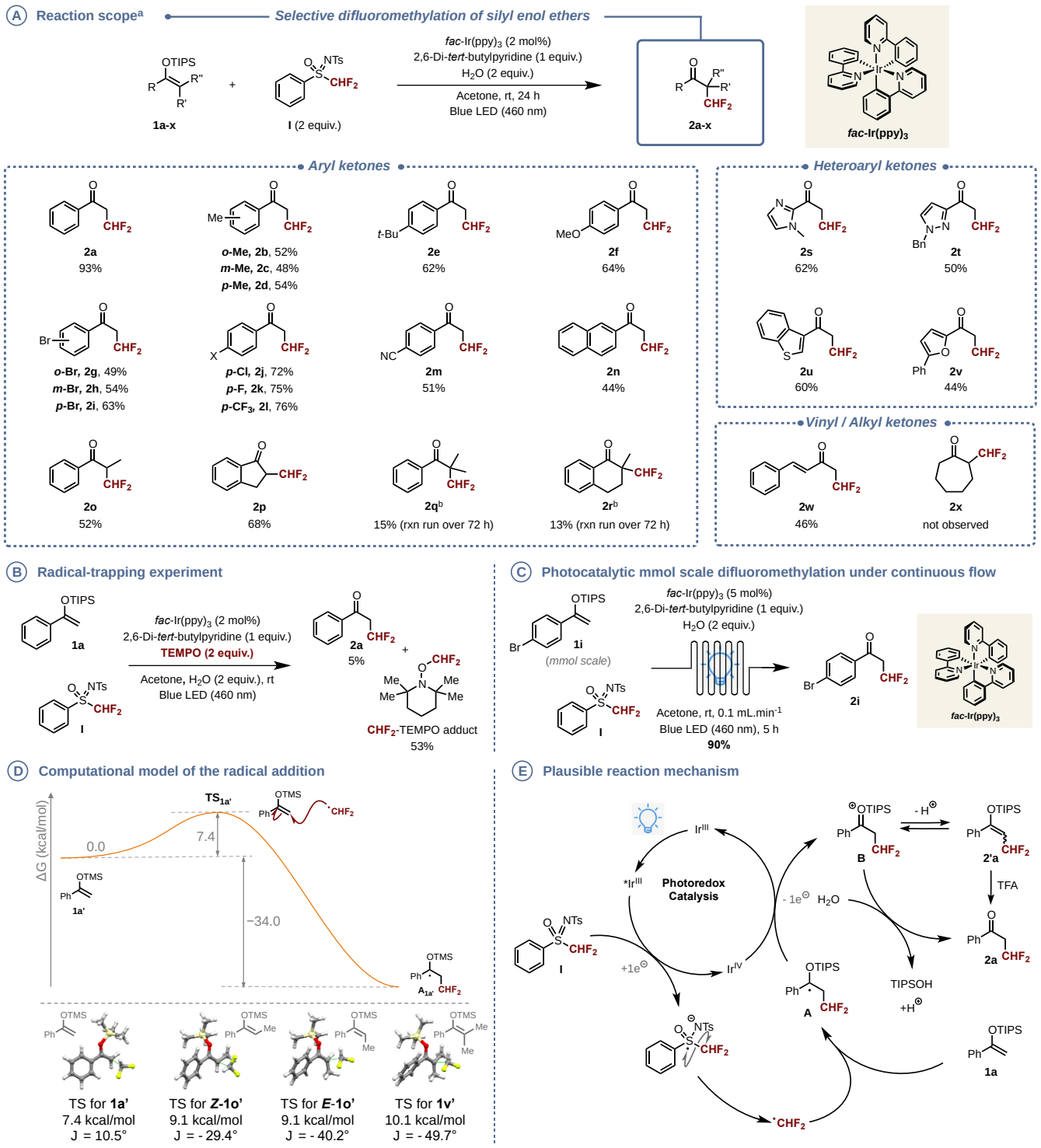


Figure 2. Full Survey [[a] **Conditions: 1** (0.2 mmol, 1 equiv.), **I** (0.4 mmol, 2 equiv.), *fac*-Ir(ppy)$_3$ (4 μmol, 2 mol%), base (0.2 mmol, 1 equiv.), H_2O (0.4 mmol, 2 equiv.), solvent (2 mL), rt, 24 h under an argon atmosphere, 8 W blue LED (460 nm), isolated yields. [b] Reaction run over 3 days instead of 24 h. [θ: dihedral angle between the planes of the phenyl and enol fragments].

Based on the available literature precedents,[18,21] we initially hypothesized that the difluoromethylation reaction was mediated by the *in situ* generation of a CHF_2 radical from **I** upon a one-electron reduction by the excited catalyst. To confirm this, we ran fluorescence quenching experiments using either **I** or **1a** as the quencher, which showed compound **I** to be a far more efficient quencher (see SI for more details). In addition, a reaction between **1a** and **I** in the presence of TEMPO under otherwise identical conditions resulted after 24 h in the formation of only 5% of the α-difluoromethylated ketone **2a** along with 53% of the TEMPO-CHF_2 adduct (Figure 2, **B**). These data strongly support an oxidative quenching pathway resulting in a one-electron reduction of **I** and subsequent decomposition releasing the CHF_2 radical.

We also studied the radical addition onto the silyl enol ether by DFT using the PBE0 functional with Grimme D3

dispersion corrections, SMD solvent model for acetone as implemented in Gaussian 16,[25] and the trimethylsilyl analogue of **1a**, **1o** and **1q** as a conformationally simplified model substrate. Our model (Figure 2, **D**) reflects a highly exergonic addition ($\Delta G = -34.0$ kcal/mol) mediated by an early, readily accessible transition state ($\Delta G^{\ddagger} = 7.4$ kcal/mol, 2.58 Å C–CHF_2 distance). These data are consistent with a rapid and irreversible radical addition. Furthermore, our model correctly anticipates the decrease in reactivity caused by the presence of α-substituents (*e.g.* propiophenone- and isubutyrophenone-derived silyl enol ethers **3o** and **3q**) due to less accessible transition states. The effect of the substituents at the α position seems to relate to an intramolecular steric repulsion that causes a loss of planarity of the aromatic ring and consequent loss of conjugation. This is consistent with the good yield obtained experimentally with **1p**, in which the α-substituent forms a bicyclic system with the aromatic ring thus maintaining a coplanar arrangement with the enol. Finally, our calculations predicted that the ketyl radical **B** resulting from the addition was a reasonably good reductant, with a reduction potential for its corresponding silyloxonium (**C**) of $E_C = -0.23$ V (all potentials reported *vs* SCE).[26] This enables its easy oxidation by the oxidised form of the catalyst $Ir(ppy)_3^+$ ($E_{Ir+} = +0.77$ V), closing the photoredox catalytic cycle. In sharp contrast, **C** is not strong enough of a reductant to propagate a chain reaction through single electron transfer with compound **I** ($E_I = -2.26$ V). This was further supported by an intermittent irradiation experiment, which showed the reaction only to occur during irradiation and abruptly stop in the absence of light (see SI for more details).

We therefore propose the following mechanism (Figure 2, **E**), where the excited $*Ir(ppy)_3$ catalyst transfers an electron to **I**, promoting its decomposition to the CHF_2 radical in conjunction with *N*-tosylsulfimate, which may be subsequently protonated. Then, addition of the electrophilic CHF_2 radical onto the silyl enol ether affords the corresponding ketyl radical **A** which is in turn oxidised by $Ir(ppy)_3^+$ to generate the silyloxonium species **B**. The latter ultimately undergoes desilylation to afford the desired ketone product **2a** with the base acting as a proton acceptor. Alternatively, α-deprotonation can also occur to afford the difluoromethylated silyl enol ether **2'a**, which was observed in several cases and could be isolated (see SI for more details). Nonetheless, **2'a** can be quantitatively hydrolyzed to the desired ketone upon workup with TFA (4 equiv.).

With the aim of scaling up the reaction, we immediately became interested in developing a continuous flow process.[27] Indeed, the narrow width of the flow reactor coil would ensure a more uniform distribution of the light within the entire reaction mixture, which would in turn increase the effective concentration of active catalyst and therefore result in shorter reaction times and improved scalability, not to mention the reduced safety concerns that are usually associated with flow chemistry. A first experiment run with **1i** (0.1 mmol scale) under our previously optimised conditions [2 equiv. of **I**, 2 mol% of *fac*-$Ir(ppy)_3$, 2 equiv. of H_2O, acetone, rt, 8 W Blue LED (460 nm), 10 mL PFA coil (Ø = 1 mm), 0.1 mL.min^{-1} flow rate (residence time = 1.7 h)] afforded the corresponding α-difluoromethyl ketones **2i** in 34% NMR yield, which compared favourably with the result obtained under the standard batch conditions over 24 h. After fine-tuning the catalyst loading (5 mol% instead of 2 mol%) and the reaction concentration (0.05 M instead of 0.1 M), we were able to maintain a low reaction time and reach up to 91% yield. These conditions were eventually applied to convert 1 mmol of **1i** in only 5 h and 90% isolated yield (Figure 2, **C**).

In summary, we have developed a straightforward method for the direct difluoromethylation of enol silanes through a visible-light-driven photoredox catalytic process. The method affords the corresponding α-CHF_2 substituted ketones in good to excellent yields under mild conditions. Moreover, the method is practical and readily scalable under continuous flow conditions. Most importantly, these α-difluoromethylated ketones are useful building blocks, which have already been shown to undergo various post-functionalizations such as α-brominations, asymmetric reductions, hydrations, acetal dehydrofluorinations, halohydrin formations, and amidations,[18-20] thus offering great perspectives for medicinal chemistry applications.

ASSOCIATED CONTENT

Supporting Information

The Supporting information is available free of charge on the Publications website. Details of experimental procedures, ^1H, ^{13}C and ^{19}F NMR spectra, HPLC chromatograms and detailed computational data.

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Notes

The authors declare no competing financial interest.

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