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Photoredox-Catalyzed Intramolecular Difluoromethylation of *N*-Benzylacrylamides Coupled with a Dearomatizing Spirocyclization: Access to CF_2H-Containing 2-Azaspiro[4.5]deca-6,9-diene-3,8-diones

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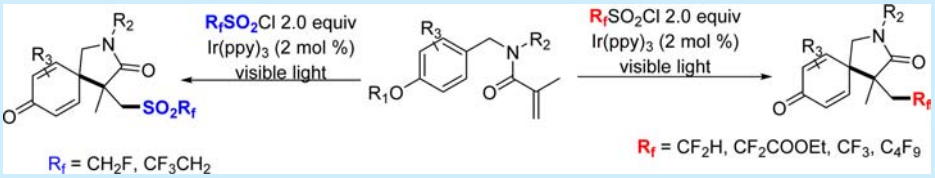
Supporting Information

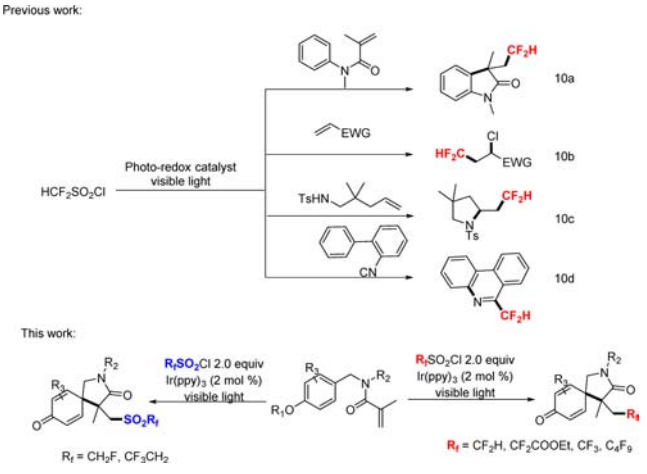


ABSTRACT: A visible light-mediated difluoromethylation of *N*-benzylacrylamides with HCF_2SO_2Cl as the HCF_2 radical precursor is described. The reaction incorporates a tandem cyclization/dearomatization process to afford various difluoromethylated 2-azaspiro[4.5]deca-6,9-diene-3,8-diones bearing adjacent quaternary stereocenters under mild conditions in moderate to excellent yields.

Organofluorine compounds have found wide application within pharmaceutical, agrochemical, and materials research due to their unique physical, chemical, and biological properties.[1] Thus, selective fluorination and fluoroalkylation have attracted considerable interest in recent years. Further, the development of methods for trifluoromethylation has been a key area of research over the last several decades.[2] In contrast, incorporation of difluoromethyl groups has received much less attention, although great strides have recently been made in this area.[3] Indeed, the CF_2H group has become an increasingly attractive component of drug and agrochemical design.[4] The lack of good nucleophilic or electrophilic difluoromethylation reagents has made difluoromethylation considerably more challenging than trifluoromethylation.[5] In answer to this challenge, there have been several elegant reports of difluoromethylation, mainly transition-metal-mediated or -catalyzed coupling reactions that introduce CF_2H into aromatic rings.[6] There have also been papers describing direct difluoromethylation via radical processes. For example, in 2012, the Baran group described an elegant direct C−H difluoromethylation of heteroarenes using a zinc sulfinate salt as the CF_2H radical precursor.[7] Later, Hu and co-workers developed a concise preparation of sodium difluoromethanesulfinate which was also used as a good CF_2H radical precursor.[8] However, both of these reactions require an excess amount of oxidant to generate the radical.

In recent years, visible light-driven photoredox catalysis has become recognized as an ecofriendly and powerful tool for organic synthesis.[9] Within our own group's efforts, difluoromethanesulfonyl chloride, in combination with photoredox catalysis, has provided what is arguably a more efficient method for generating the difluoromethyl radical under conditions that allowed good reactivity toward various unsaturated bonds.[10] In our work, photoredox-catalyzed radical cascade reactions have been demonstrated as an excellent approach to constructing complex organic skeletons bearing fluoroalkyl groups, in particular the difluoromethyl group (Scheme 1).

Scheme 1. Photoredox-Catalyzed Difluoromethylation of Unsaturated Bonds



Azaspirocycles are a structural feature frequently found in natural products. Indeed, azaspirocyclic cyclohexadienones are pivotal intermediates in the preparation of an extensive range of biologically active molecules.[11] Moreover, dearomatization reactions have drawn increasing attention as a powerful strategy to construct ring systems from readily available aromatic compounds.[12] The dearomatization of phenols to cyclo-

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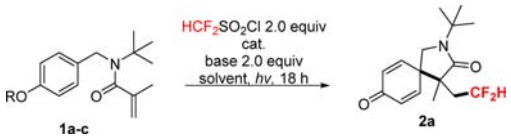
hexadienones is a process that has been used several times in complex total syntheses.[13] Several examples of radical spirocyclization onto a *p*-methoxyaryl ring have been reported.[14] In addition, the Xia group reported visible-light induced trifluoromethylation of *N*-arylcinnamamides, using Togni's reagent, which afford a variety of CF_3-containing dihydroquinolin-2(1*H*)-ones and 1-azaspiro[4.5]decanes.[15] Zhu and co-workers have used the same strategy successfully to introduce difluoroacetyl into quinoline-2-ones and 1-azaspiro[4.5]decanes.[16] Regarding 2-azaspiro[4.5]decyl systems, the Wang group has developed a copper-catalyzed intramolecular trifluoromethylation of *N*-benzylacrylamides coupled with dearomatization using the Togni reagent as the CF_3 source.[17] Until the present work, there have been no methods for introduction of the CF_2H group into this kind of azaspiro cyclic system. Consistent with our group's previous work, we hereby report our current results on the introduction of not only the difluoromethyl group but also the CF_3 group and perfluoroalkyl groups into azaspiro[4,5]decyl systems.

The reaction conditions were optimized using *N*-(4-methoxy)benzylacrylamide (**1a**) as a model substrate and difluoromethanesulfonyl chloride as the radical source (Table 1). Various solvents were initially screened, and it was found

Table 1. Optimization of Reaction Conditions[a]



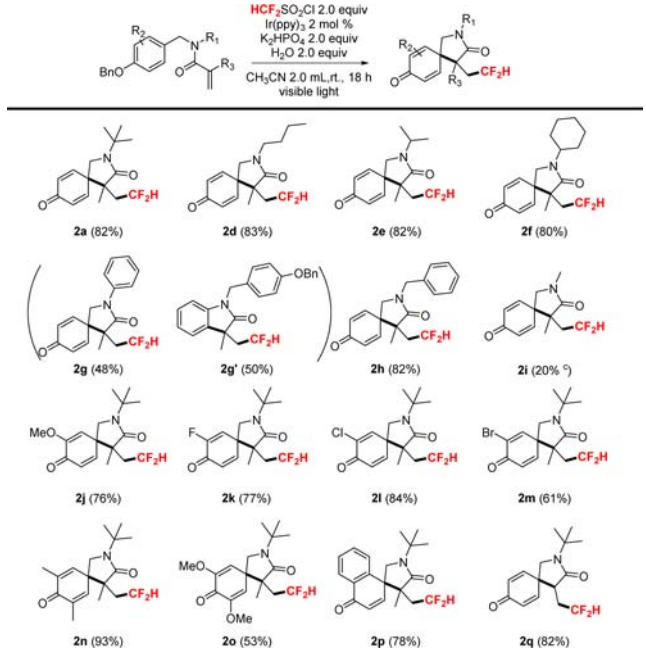
entry	catalyst	solvent	base	yield[b] (%)
1	$Ir(ppy)_3$	CH_3CN	K_2HPO_4	40
2	$Ir(ppy)_3$	dioxane	K_2HPO_4	9
3	$Ir(ppy)_3$	HOAc	K_2HPO_4	20
4	$Ir(ppy)_3$	DCE	K_2HPO_4	30
5	$Ir(ppy)_3$	CH_3CN	K_2CO_3	trace
6	$Ir(ppy)_3$	CH_3CN	Na_2CO_3	trace
7	$Ir(ppy)_3$	CH_3CN	KOAc	trace
8	$Ir(ppy)_3$	CH_3CN	NaOAc	trace
9[c]	$Ir(ppy)_3$	CH_3CN	K_2HPO_4	trace
10	$[Ir(dtbpy)\ (ppy)_2]PF_6$	CH_3CN	K_2HPO_4	44
11[d]	$Cu(dap)_2Cl$	DCE	Ag_2CO_3	21
12[e]	$Ir(ppy)_3$	CH_3CN	K_2HPO_4	50
13[e]	$Ir(ppy)_3$ (2 mol %)	CH_3CN	K_2HPO_4	80
14[e,f]	$Ir(ppy)_3$ (2 mol %)	CH_3CN	K_2HPO_4	82
15[e,g]	$Ir(ppy)_3$ (2 mol %)	CH_3CN	K_2HPO_4	81

[a]Reactions were run with 0.1 mmol of **1a** (R = Me), 0.2 mmol of HCF_2SO_2Cl, 0.2 mmol of base, and 0.001 mmol of catalyst in 1 mL of solvent under visible light. [b]All yields were based on **1a** using *N*,*N*-dimethyltrifluoroacetamide as the internal standard. [c]Reaction runs at 50 °C. [d]Reaction runs at 75 °C. [e]2.0 equiv of water as additive. [f]Substrate **1b** (R = benzyl). [g]Substrate **1c** (R = *p*-methoxybenzyl).

that when CH_3CN (entry 1) was used as solvent the desired difluoromethyl-containing product, 2-azaspiro[4.5]decane **2a**, was obtained in 40% yield as determined by ^{19}F NMR (entry 1). Encouraged by the results, we examined alternative bases in attempting to improve the yield. Unfortunately, the use of K_2CO_3, Na_2CO_3, KOAc, and NaOAc all hindered the reaction, with only trace amounts of product being detected (entries 5–8). In these experiments, considerable starting material and difluoromethanesulfonyl chloride remained after workup. Therefore, an attempt was made to promote the reaction by raising the temperature. However, this led to no product being formed, with most of the sulfonyl chloride being destroyed by the base (entry 9). Reasoning that the low yield was due to ineffective oxidation of the intermediate cyclohexadienyl radical, other catalysts were tried. $[Ir(dtbpy)\ (ppy)_2]PF_6$ give a somewhat higher yield, but $Cu(dap)_2Cl$ only afforded 21% of product (entries 10 and 11). Water was added to the reaction mixture (entry 12) with the hope of increasing the polarity of the medium and thus stabilizing the desired carbocation intermediate, and the desired reaction was enhanced, giving 50% yield of product. By increasing the amount of catalyst to 2 mol % under these condition the yield was increased to 80%, with all of the starting materials being consumed (entry 13). The use of alternative protecting groups on the phenol such as benzyl (**1b**) or *p*-methoxybenzyl (**1c**) also resulted in good reactivity and afforded product **1a** in very good yields (entry 14 and 15).

Using the conditions described in Table 1, entry 14, we investigated the scope of variously substituted *N*-benzylacrylamides that might be effective in this reaction (Scheme 2).

Scheme 2. Substrate Scope of Photoredox-Catalyzed Difluoromethylation/Spirocyclization[a,b]



[a]Reactions were run with 0.2 mmol of **1b**, 0.4 mmol of HCF_2SO_2CI, 0.4 mmol of base, and 0.002 mmol of catalyst in 2 mL of dioxane with 8 mg water under visible light. [b]Isolated yield. [c]Yields were determined by ^{19}F NMR using *N*,*N*-dimethyltrifluoroacetamide as internal standard.

Initially, various *N*-substituents (R_1) were examined. Those with *n*-butyl, cyclohexyl, isopropyl, or the more bulky *tert*-butyl substituent all afforded the corresponding 2-azaspiro[4.5]deca-6,9-diene-3,8-diones **2a**–**f** in very good yields. However, when an *N*-phenyl substituent was used, the reaction became more complex, and the reaction only gave 48% of the desired product **2g** along with 50% yield of a byproduct **2g′**, both of which could be isolated. This side product derived, of course, from competitive cyclization of the radical onto the *N*-phenyl substituent. Use of an *N*-benzyl substituent gave only the

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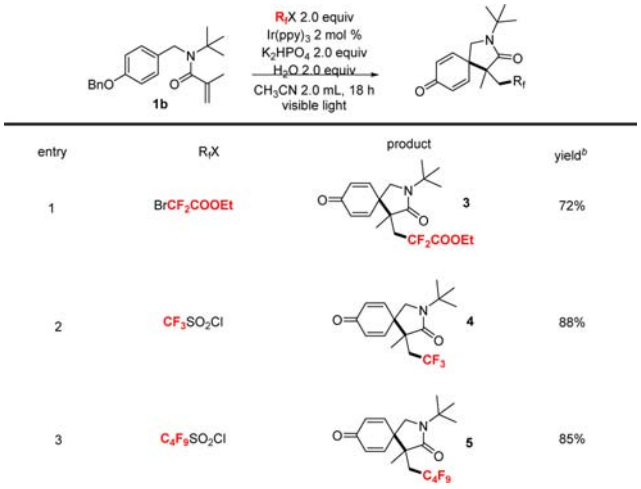
normal product, **2h**, in good yield. When a much smaller group, such as methyl, was on the nitrogen, the reaction become sluggish and only 20% of product **2i** could be detected. This indicates that the steric influence of the *N*-substituent plays an important role in facilitating the cyclization.

When substrates with various substituents R_2 on the aromatic ring were investigated, it was found that those with either electron-donating groups (i.e., methoxy) or electron-withdrawing groups such as F, Cl, or Br all react smoothly to afford products **2j**–**m** in moderate to good yield. In addition, all of the nonaxisymmetric substrates gave pairs of diastereomers in an approximately 1:1 ratio. When the phenol was replaced by a naphthol, the desired product **2p** was also obtained in good yield. Interestingly, in contrast to our previous report on cyclizations of phenylacrylamides (Scheme 1),[10a] acrylamide **1q** without the α-methyl substituent (R_3 = H) proved to be a good substrate in this reaction, producing desired product **2q** in 83% yield.

In order to develop a unified strategy to introduce various fluoroalkyl groups into the azaspiro ring system, other sulfonyl chlorides were also investigated (Scheme 3). Since

Scheme 3. Photoredox-Catalyzed Difluoromethylation/Dearomatization with Other Fluoroalkyl Radical Sources[a]

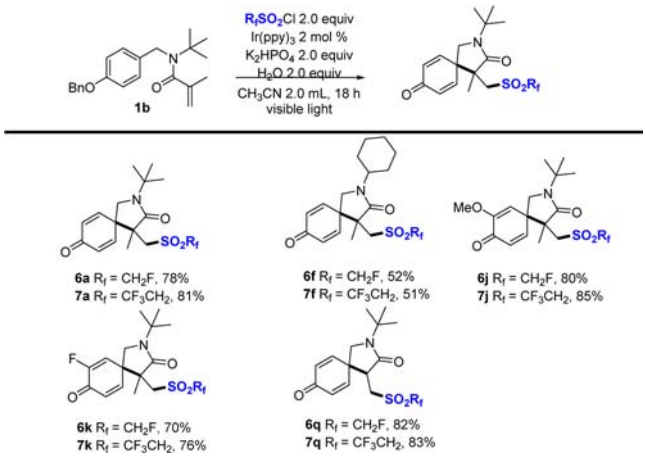


[a]Reactions were run with 0.2 mmol of **1b**, 0.4 mmol of HCF_2SO_2Cl, 0.4 mmol of base, and 0.002 mmol of catalyst in 2 mL of CH_3CN with 8 mg of water under visible light. [b]Isolated yield.

$BrCF_2COOEt$ is commercially available and also had been proved to be efficiently reduced by the photoredox catalyst, this bromide was used as the CF_2COOEt radical source, which in the event produced the desired, analogous product **3** in good yield. Then it was shown that both CF_3SO_2Cl and $C_4F_9SO_2Cl$ gave their corresponding products, **4** and **5**, in very good yield.

To our surprise, when CH_2FSO_2Cl and $CF_3CH_2SO_2Cl$ were used as radical sources, the only products to be observed were products that had retained the SO_2 group, **6** and **7**, which were obtained in good yield (Scheme 4). This result can be contrasted with the results in our previous report when we used these same sulfonyl chlorides, where the SO_2 was lost.[10a] We reasoned that the smaller electronegativity of the CH_2F and CF_3CH_2 groups would make the loss of SO_2 more difficult. Thus, under the present room temperature reaction conditions, SO_2 was not eliminated. (The reactions with these sulfonyl chlorides in the earlier report were carried out at 105 °C.)

Scheme 4. Substrates Scope with SO_2 Group Retained[a,b]

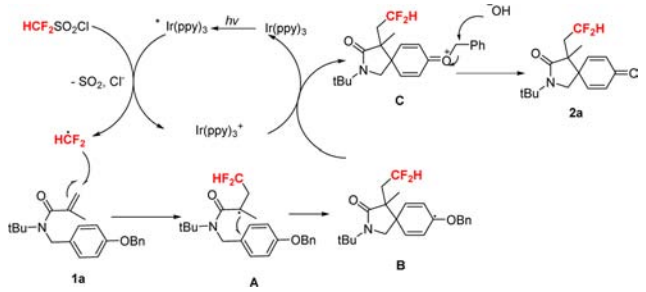


[a]Reactions were run with 0.2 mmol of **1**, 0.4 mmol of R_fSO_2Cl, 0.4 mmol of base, and 0.004 mmol of catalyst in 2 mL of CH_3CN with 8 mg of water under visible light. [b]Isolated yield.

Considering the contrasting results, the reaction was attempted at 105 °C, using DCE as solvent, but unfortunately, no desired product was formed. It appears that at the higher temperature (see Table 1, entry 9) the sulfonyl chlorides were quickly destroyed by the base. A few substrates were also examined using these sulfonyl chlorides, and both provided the sulfonyl products (**6** and **7**) in medium to very good yields.

The proposed mechanism for these reactions is shown in Scheme 5. First, the sulfonyl chloride is reduced by the excited

Scheme 5. Proposed Mechanism



Ir catalyst forming the difluoromethyl radical. Then the radical attacks the double bond to form intermediate radical **A**, which would quickly undergo cyclization to form the intermediate radical **B**. Intermediate B is then oxidized by the hyper Ir catalyst to form intermediate cation **C**, regenerating the catalyst. The water might stabilize carbocation **C** and thus promote the catalytic cycle. Finally, water under the basic conditions reacts with the carbocation to form the product.

In conclusion, a photoredox-catalyzed cascade reaction involving difluoromethylation of substituted *N*-benzylacrylamides, 5-exo cyclization, and resultant dearomatization has been described. It is the first example of introduction of the difluoromethyl group into the azaspiro ring system. This reaction also supplied a unified strategy to introduce other fluoroalkyl groups into spirocyclohexadienones bearing adjacent quaternary stereocenters under mild conditions in good to excellent yield. Considering the wide substrate scope and simple procedure, this reaction should be useful for the

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preparation of a host of potential medicinal and agrochemical agents.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00168.

Experimental procedures, compound characterization data, and NMR spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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