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Photoredox-Catalyzed Intramolecular Aminodifluoromethylation of Unactivated Alkenes

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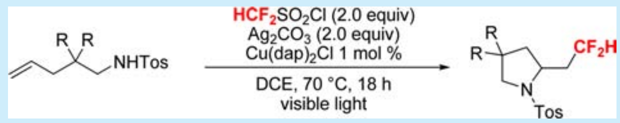
Supporting Information

ABSTRACT: A photoredox catalyzed aminodifluoromethylation of unactivated alkenes has been developed in which HCF_2SO_2Cl is used as the HCF_2 radical source. Sulfonamides were active nucleophiles in the final step of a tandem addition/oxidation/cyclization process to form pyrrolidines, and esters were found to cyclize to form lactones. Thus, a variety of pyrrolidines and lactones were obtained in moderate to excellent yield. In order for the cyclization reactions to be efficient, a combination of a copper catalyst (Cu(dap)$_2$Cl) and silver carbonate was crucial to suppressing a competing chloro, difluoroalkylation process.

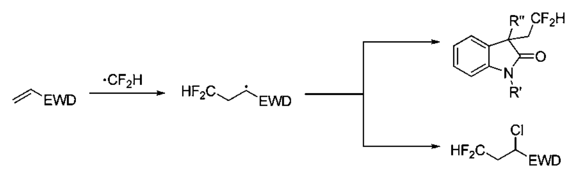


Properties of organic molecules, such as metabolic stability, bioavailability, lipophilicity, and membrane permeability, play a crucial role in defining the efficacy of agrochemicals, pharmaceuticals, and biomaterials.[1] Among the commonly encountered fluoroalkyl groups, difluoromethyl has drawn increasing attention,[2] in part because CF_2H can act as a more lipophilic hydrogen bond donor than typical donors such as OH and NH.[3] In addition, compared with CF_3, the methods available to introduce CF_2H into organic compounds are relatively limited.[4] Recently much elegant difluoromethylation work had been reported, which mainly focused on constructing difluoromethyl arenes and heteroarenes.[5] Nonaromatic heterocycles such as pyrrolidine are also of synthetic interest, such structures being present in a wide variety of naturally occurring and biologically active molecules.[6] As a result the development of efficient methods for the incorporation of CF_2H into pyrrolidines is a subject worthy of attention.

Recently numerous papers reporting methods of difunctionalization of alkenes have appeared.[7] In addition, intramolecular difunctionalizations of olefins, including aminohalogenation, carboamination, and oxyamination, have offered an efficient strategy for the introduction of various functional groups while constructing such heterocycles.[8] Aminofluorinations have also been realized.[9] Regarding fluoroalkylations, Buchwald's group reported in 2012 the oxytrifluoromethylation of unactivated alkenes using Togni's reagent combined with a copper catalyst.[10] In 2014 Liu's group, using a similar strategy, was successful in observing aminotrifluoromethylation.[11]

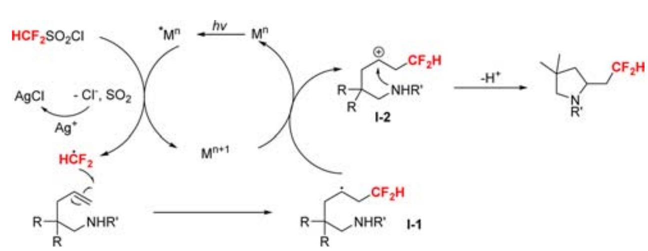
With the lack of a good electrophilic difluoromethylation reagent, it has remained a challenge to carry out difluoromethylations in a similar manner. However, our research group has recently focused efforts on the use of fluoroalkylsulfonyl chlorides for the purpose of introduction of fluoroalkyl groups, via initial alkene addition. In particular, the CF_2H radical generated from single electron reduction of CF_2HSO_2Cl by a photoredox catalyst has been shown to have excellent reactivity toward electron-deficient alkenes. The radical formed by such additions could either undergo cyclization with an aromatic ring or form a carbon−chlorine bond through an ATRA process (Scheme 1).[12,13]

Scheme 1. Photoredox Catalyzed Difluoromethylation Reactions



In this paper, we wish to report a photoredox catalyzed intramolecular aminodifluoromethylation of unactivated alkenes under mild conditions. In designing this study our hypothesis was that the CF_2H radical should initially react with alkenes to form an alkyl radical, which can then be oxidized by the catalyst to form a carbocation, which can then itself be trapped intramolecularly by a not readily oxidizable nucleophile, such as the nitrogen of a sulfonamide to produce a difluoromethylated pyrrolidine, as shown in the mechanistic scheme below (Scheme 2).

Scheme 2. Probable Mechanism



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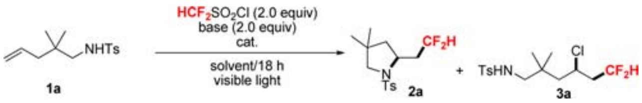
To test our hypothesis we chose sulfonamide **1a** as a model substrate that could be used to optimize reaction conditions (Table 1). Initially, for the reaction with CF_2HSO_2Cl,

Table 1. Optimization of Reaction Conditions[a]



entry	cat.	base	temp/°C	yield[b]
1[c]	1 mol % $Ir(ppy)_3$	Na_2CO_3	rt	ND (26%)
2[c]	1 mol % $Ir(ppy)_3$	K_2HPO_4	rt	ND (60%)
3[c]	1 mol % $Ir(ppy)_3$	Ag_2CO_3	rt	ND (59%)
4[c]	1 mol % $Ir(ppy)_3$	Cs_2CO_3	rt	ND
5	0.75 mol % $Cu(dap)_2Cl$	Na_2CO_3	90	28% (33%)
6	0.75 mol % $Cu(dap)_2Cl$	K_2CO_3	90	9% (11%)
7	0.75 mol % $Cu(dap)_2Cl$	Cs_2CO_3	90	ND
8	0.75 mol % $Cu(dap)_2Cl$	K_2HPO_4	90	19% (20%)
9	0.75 mol % $Cu(dap)_2Cl$	K_3PO_4	90	33% (39%)
10	0.75 mol % $Cu(dap)_2Cl$	NaOAc	90	28% (31%)
11	0.75 mol % $Cu(dap)_2Cl$	KOAc	90	14% (16%)
12	0.75 mol % $Cu(dap)_2Cl$	Ag_2CO_3	100	50% (trace)
13	1 mol % $Cu(dap)_2Cl$	Ag_2CO_3	70	76% (trace)
14	0.3 mol % $Cu(dap)_2Cl$	Ag_2CO_3	70	51% (trace)

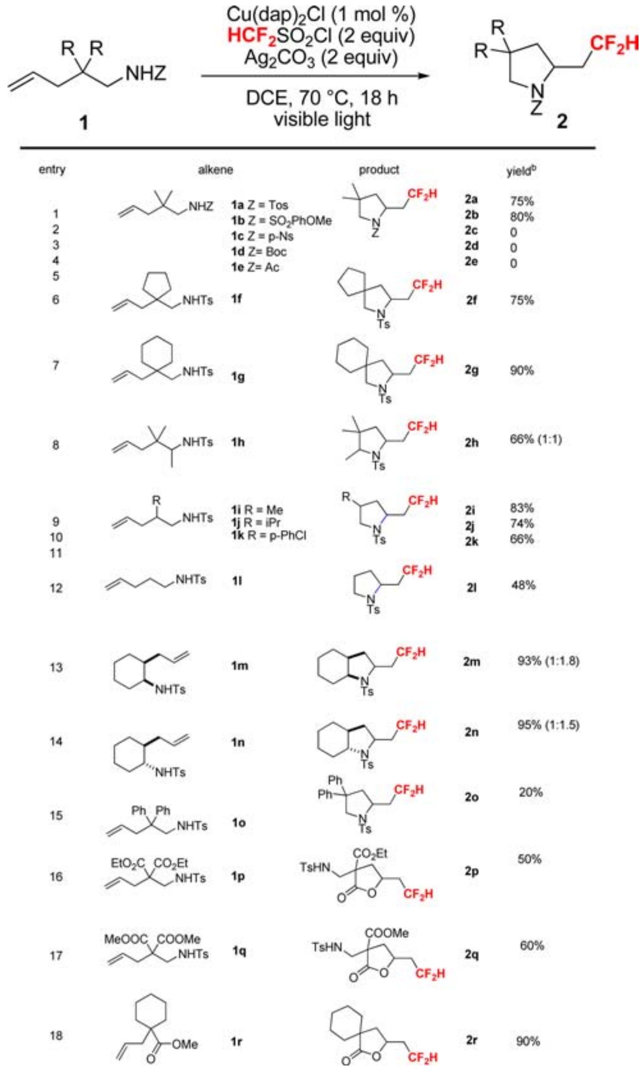
[a]Reactions were run with 0.1 mmol of **1a**, 0.2 mmol of CF_2HSO_2Cl, 0.2 mmol of base, and 0.0001 mmol of catalyst in 1 mL of DCE. All yields were based on **1a** using $CF_3CON(Me)_2$ as the internal standard. [b]Values in parentheses are yields of chloro, difluoromethylation addition products. [c]CH_3CN as solvent.

$Ir^{III}(ppy)_3$ was tried as the catalyst in CH_3CN as solvent, using various bases under visible light (entries 1−4). Unfortunately only the chloro, difluoromethylation (addition) product was detected, instead of cyclization, which suggested that $Ir^{IV}(ppy)_3Cl$ could not oxidize the carbon radical intermediate efficiently. In the absence of oxidation, the carbon radical abstracted the chlorine atom from CF_2HSO_2Cl to propagate the simple addition reaction. Several reports indicate that copper catalysts can be superior to $Ir(ppy)_3$ for this oxidation step. Therefore, it was decided to examine $Cu(dap)_2Cl$ as the photoredox catalyst. Even though this catalyst has a lower oxidation potential compared with $Ir(ppy)_3$,[14] it had earlier been shown to be efficient in the reductive step to generate the CF_2H radical from HCF_2SO_2Cl.

Whereas, no cyclization had been observed when using the Ir catalyst, 28% of the cyclization product was observed along with 33% of the addition product in the initial experiment using $Cu(dap)_2Cl$ in DCE with $NaCO_3$ as the base at 90 °C (entry 5). To improve the yield and to suppress the chlorine addition product, Ag_2CO_3 was added to the reaction (entry 13), and as a result only trace amounts of the chlorine addition product was observed, and the reaction gave the desired **2a** as the major product in 50% yield. Finally by lowering the temperature and increasing the amount of catalyst to 1 mol %, the reaction displayed good chemoselectivity, giving a single product **2a** in 76% yield (entry 14).

Using this optimized protocol, the substrate scope was examined (Scheme 3). The protecting group on nitrogen proved to have a significant effect upon its efficacy in the reaction. It was found that *p*-methoxybenzene-sulfonamide (**1b**) was a slightly better substrate, but that the more electron-deficient *p*-nitrobenzenesulfonamide (nosyl) substrate gave no

Scheme 3. Substrate Scope[a]



[a]Reactions were run with 0.2 mmol of **1a**, 0.4 mmol of CF_2HSO_2Cl, 0.4 mmol of base, and 0.0002 mmol of catalyst in 2 mL of solvent. [b]Isolated yield.

observable cyclization. Also, carboxamides, such as Boc (**1d**) and acetamide (**1e**), were ineffective substrates.

Then other substrates with *gem*-substituents (**1f** and **1g**) were tested, with these reactions also proceeding smoothly to provide product **2f** and **2g** in good yield. When a substituent was introduced to the position *α* to nitrogen, the yield of the product (**2h**) was lowered slightly. Monosubstituted substituents or those without *gem*-substituents substrates **1i**−**1l** were also compatible with the reaction conditions, delivering products **2i**−**2l** in moderate to good yield. Furthermore, both *cis*- and *trans*-cyclohexyl substrates **1m** and **1n** proceeded very well to provide products **2m** and **2n** in excellent yield, as a mixture of diastereomers. However, a substrate with *gem*-diphenyl substituents (**1o**) proved to be a reluctant reactant, with only 20% of product being obtained.

To our surprise, when substrates with *gem*-diester substituents **1p** and **1q** were examined, the lactone products **2p** and **2q** were isolated instead of the expected pyrrolidine. This seemed to indicate that ester carbonyls are better nucleophiles in the reaction than a sulfonamide nitrogen. Consistent with

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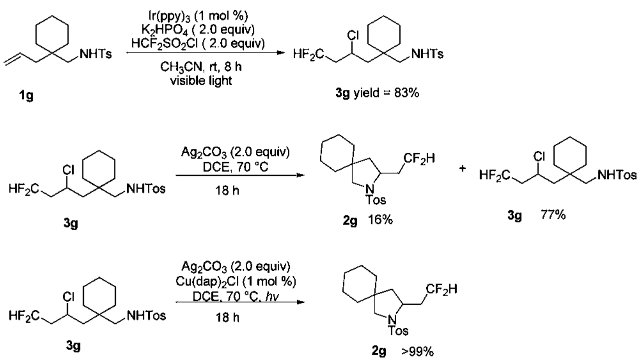
this supposition, ester **1r** was an excellent substrate, producing lactone (**2r**) in excellent yield.

Since the chlorine addition product had been a significant side product in the absence of $AgCO_3$, a stepwise process was considered to be a mechanistic possibility. When the chlorine addition product (**3g**) was synthesized (Scheme 4) and then

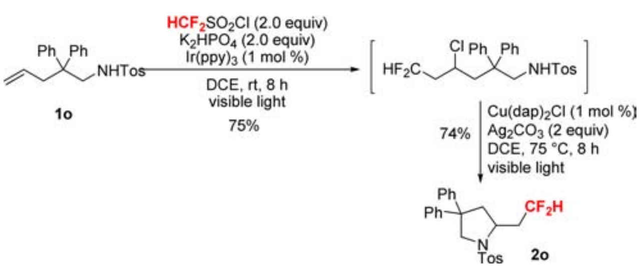
Scheme 4. Probe of Mechanism



treated with 2.0 equiv of silver carbonate under the same reaction conditions, only 16% of the cyclization product was formed, with 77% of the starting material remaining. However, when 1 mol % $Cu(dap)_2Cl$ was added to the reaction mixture, conversion of **3g** was complete. What all of this indicates is that, under the optimized conditions, either pathway (one or two step) to eventual cyclized product can be effective, and the two pathways are likely competing.

Sometimes using a clear two-step procedure may be preferred over the "one pot" method. For example, when the two-step procedure was used for *gem*-diphenyl substrate **1o**, product **2o** was obtained in a significantly higher overall yield than when the one-pot procedure was used (Scheme 5).

Scheme 5. Two-Step Example



Unfortunately, the scope of this reaction could not be further expanded to the use of n-$C_4F_9SO_2Cl$, CF_3SO_2Cl, or FCH_2SO_2Cl as radical sources. Within our experience, none of these sulfonyl chlorides led to satisfactory addition/oxidation/cyclization chemistry under identical or related reaction conditions. Presumably, the oxidation of radical intermediate **I-1** to carbocation **I-2** (Scheme 2) was inhibited by the presence of the more electronegative n-C_4F_9 and CF_3 groups. As a result, use of n-$C_4F_9SO_2Cl$ and CF_3SO_2Cl led to good yields of the products of the simple ATRA addition reactions, in 77% and 76% yields, respectively. Use of FCH_2SO_2Cl in the reaction led to a low yield (15%) of desired product, probably due to its lower ability to be reduced by the catalyst.

In conclusion, CF_2HSO_2Cl can be used as a source of the difluoromethyl radical to carry out efficient photoredox catalyzed intramolecular amino- and oxy-difluoromethylation reactions of unactivated alkenes. In order for the cyclization reactions to be efficient, a copper catalyst ($Cu(dap)_2Cl$) in combination with silver carbonate was crucial to suppressing the competing chloro, difluoroalkylation process. Using this procedure, a variety of pyrrolidines could be efficiently synthesized in moderate to excellent yield. Esters exhibited even greater nucleophilic reactivity to prepare lactones in very good yield.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization and NMR spectra of new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01616.

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Notes

The authors declare no competing financial interest.

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