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Difluoromethylsulfonyl Imidazolium Salt for Difluoromethylation of Alkenes

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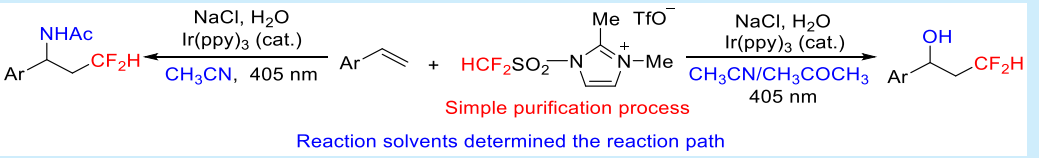
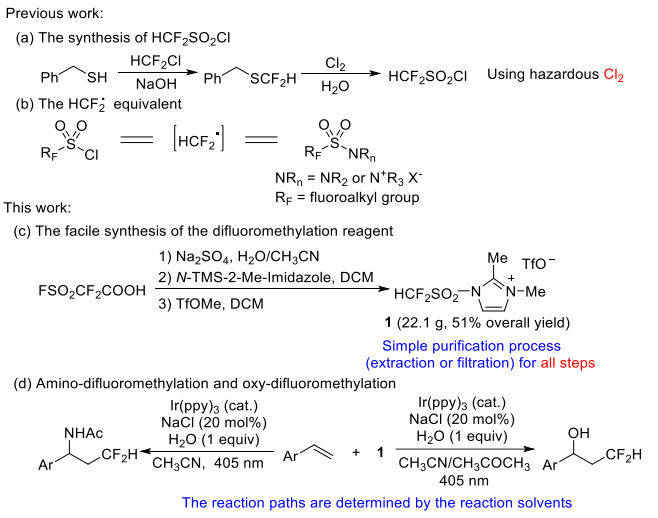


ABSTRACT: Herein, we describe the design and synthesis of a difluoromethylsulfonyl imidazolium salt, which can act as a radical difluoromethylation reagent to achieve the challenging amino- and oxy-difluoromethylation of alkenes. Notably, the three steps for the synthesis of the imidazolium salt do not require any tedious distillation or column chromatography purification process, and the amino- and oxy-difluoromethylation paths are simply determined by the selection of reaction solvents.

The unique properties of the fluorine element, such as high electronegativity and small atomic radius, may endow fluorinated groups with some "magic" effects.[1] The difluoromethyl group (HCF_2), which can act as a lipophilic hydrogen bond donor and as a bioisostere of hydroxyl and thiol groups,[2] is of particular interest in agrochemistry and pharmaceutical chemistry. A large number of HCF_2-containing pharmaceuticals and agrochemicals have been developed, including deracoxib, roflumilast, isopyrazam, and bixafen.[3] The intriguing features of the HCF_2 group led to extensive studies of the effective installation of a HCF_2 group into organic molecules.[3,4] Many difluoromethylation reagents have been developed,[5] including $TMSCF_2H$,[6] L_n-M-CF_2H (M = Cu, Ag, etc.),[7] HCF_2SO_2Cl,[8] and $[Ph_3P^+CF_2H]Br^-$.[9] However, some limitations of these reagents, such as their high volatility or the need for the use of a transition metal element embeded in reagents, stimulate further development of difluoromethylation reagents.

Fluoroalkylsulfonyl chlorides (R_FSO_2Cl, R_F = HCF_2 or CF_3) have served as versatile fluoroalkylation reagents because the SO_2−Cl bond can be easily cleaved to generate fluoroalkyl radicals under reductive conditions.[8,10] Our experiences in CF_3SO_2Cl[11] encouraged us to explore the synthetic utility of HCF_2SO_2Cl. However, the synthesis of HCF_2SO_2Cl requires the use of a hazardous gas, elemental chlorine (Cl_2) (Scheme 1a).[8] Furthermore, the high volatility of HCF_2SO_2Cl may limit the applications of this reagent. Because the reductive cleavage of $(R_F)SO_2$−$N(R_n)$ bonds could also produce fluoroalkyl radicals, as evidenced by recent reports independently described by us[12] and other groups,[13] it is reasonable to speculate that a difluoromethylsulfonyl imidazolium salt may also act as a $HCF_2^•$ radical equivalent. We then designed a facile synthetic route to difluoromethylsulfonyl imidazolium salt **1** (Scheme 1c). Notably, none of these three steps requires

Scheme 1. Difluoromethylation Reagents and Difluoromethylation of Alkenes



a tedious purification process, such as distillation or flash column chromatography. A convenient workup process for each step, such as extraction or filtration, can give the final pure salt on a large scale. The successful synthesis of salt **1** allowed us to investigate the difluoromethylative bifunctionalization of

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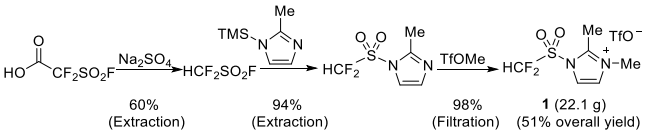
alkenes (Scheme 1d). Because the bifunctionalizations can incorporate a second group, which may also be a valuable moiety for drug design or permit further transformations, significant efforts have been devoted to the study of bifunctionalizations, such as hydro-difluoromethylation,[14] carbo-difluoromethylation,[9d,15] and halo-difluoromethylation.[8b,9a,16] Despite these outstanding accomplishments, oxy-difluoromethylation[17] and amino-difluoromethylation[18] of alkenes remain challenging. In this work, the NHAc group in the amino-difluoromethylation products is derived from acetonitrile, and the OH group of the oxy-difluoromethylation products is derived from water. It is worth mentioning that the reaction paths are determined by the reaction solvents. Acetonitrile and acetonitrile/acetone lead to amino-difluoromethylation and oxy-difluoromethylation, respectively.

The difluoromethylsulfonyl imidazolium salt (**1**) was synthesized via a three-step process, decarboxylation, SO_2−N bond formation, and quaternization of the imidazole, starting from $HO_2CCF_2SO_2F$, a reagent developed by the group of Chen[19] (Scheme 2). The sequential steps do not require any tedious workup procedures. Distillation and column chromatography can both be avoided, and pure salt **1** could be obtained on a large scale in a moderate overall yield (22.1 g, 51%).

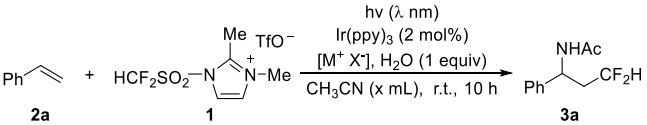
Scheme 2. Synthesis of Difluoromethylsulfonyl Imidazolium Salt 1



With imidazolium salt **1** in hand, we then screened the reaction conditions for the photoredox-catalyzed amino-difluoromethylation of alkene **2a** by using $Ir(ppy)_3$ as a photocatalyst (Table 1). We conceived that salt **1** may need to be converted in situ into a difluoromethylsulfonyl halide (HCF_2SO_2X, X = Cl, Br, or I), which is more reactive and thus could be easily reduced. Therefore, various halide anions ($[M^+X^-]$) were examined (entries 1−5). Both Br^- and I^- anions were ineffective (entries 1 and 2, respectively), probably because the HCF_2SO_2Br and HCF_2SO_2I intermediates are highly reactive. To our delight, a 42% yield was obtained by using NaCl as a chloride source (entry 5). No superior effect was observed by using cosolvents (entries 6−8), but an oxy-difluoromethylation product was obtained in 75% yield when acetone was used as a cosolvent (entry 8), which prompted us to further investigate the oxy-difluoromethylation of alkenes, as shown in Scheme 4. Although $Ir(ppy)_3$ undergoes photoexcitation at a λ_{max} of 375 nm,[20] an examination of wavelengths (entries 9 and 10) revealed that the reaction mixture irradiated at 405 nm gave a higher yield (entry 10 vs entry 9). The loading of NaCl (entries 11−13) could be decreased to 0.2 equiv (entry 13). The concentration also played a role (entries 13−15), and a high yield was obtained at a substrate concentration of 0.1 mol/L (entry 15). The yield was not increased with an increase in the loading of reagent **1** (entry 16). Increasing the loading of H_2O led to a decrease in the yield (entries 17 and 18).

With the optimal conditions in hand (Table 1, entry 15), we then investigated the substrate scope of the amino-difluoromethylation of alkenes with salt **1**. As shown in Scheme 3, the amino-difluoromethylation process could be extended to a wide range of aryl alkenes, and almost no oxy-difluoromethylation byproduct was detected in each case. Various functional groups could be tolerated, such as nitrile, boronic ester, aldehyde, and ester groups. The compatibility of the reactive Bpin with this reaction could allow for the further diversification of the product (**3n**). Electron-rich, -neutral, and -deficient aryl alkenes could all be converted into the desired products in moderate to high yields. This process is not applicable to aliphatic alkenes.

Table 1. Screening the Reaction Conditions for the Amino-difluoromethylation of Alkene 2a[a]



entry	$[M^+X^-]$	**2a**:**1**:$[M^+X^-]$[b]	λ (nm)	x (mL)	yield (%)[c]
1	NaBr	1:1.5:1	455	1.5	0
2	NaI	1:1.5:1	455	1.5	0
3	NH_4Cl	1:1.5:1	455	1.5	0
4	$^nBu_4NCl$	1:1.5:1	455	1.5	0
5	NaCl	1:1.5:1	455	1.5	42
6[d]	NaCl	1:1.5:1	455	0.5	23
7[e]	NaCl	1:1.5:1	455	0.5	43
8[f]	NaCl	1:1.5:1	455	0.5	0
9	NaCl	1:1.5:1	370	1.5	51
10	NaCl	1:1.5:1	405	1.5	73
11	NaCl	1:1.5:2	405	1.5	73
12	NaCl	1:1.5:0.5	405	1.5	75
13	NaCl	1:1.5:0.2	405	1.5	76
14	NaCl	1:1.5:0.2	405	1	50
15	NaCl	1:1.5:0.2	405	2	84
16	NaCl	1:2:0.2	405	2	83
17[g]	NaCl	1:1.5:0.2	405	2	78
18[h]	NaCl	1:1.5:0.2	405	2	75

[a]Reaction conditions: substrate **2a** (0.2 mmol), **1**, $Ir(ppy)_3$ (2 mol %), $[M^+X^-]$, and H_2O (1 equiv) in CH_3CN at room temperature for 10 h under the irradiation of LED lights under a N_2 atmosphere. [b]Molar ratio. [c]The yields were determined by ^{19}F NMR spectroscopy. [d]With 1 mL of CH_2Cl_2 as a cosolvent. [e]With 1 mL of EtOAc as a cosolvent. [f]With 1 mL of acetone as a cosolvent, and an oxy-difluoromethylation product (**4a**) obtained in 75% yield. [g]With 1.5 equiv of H_2O. [h]With 2 equiv of H_2O.

As shown in Table 1, oxy-difluoromethylation product **4a** was detected when acetone was used as a cosolvent. After a further brief examination of the reaction conditions (see the Supporting Information), it was found that the use of a 1:1 (v/v) CH_3CN/CH_3COCH_3 mixture as the reaction solvent almost completely suppressed the amino-difluoromethylation and afforded the oxy-difluoromethylation product in a good yield. A wide substrate scope and good functional group tolerance were observed for the oxy-difluoromethylation (Scheme 4). The reactive boronic ester group also remained intact under these conditions (**4n**). Irrespective of whether an electron-rich or an electron-deficient group is attached to the aryl ring, all of the aryl alkenes could undergo the expected transformations smoothly. Aliphatic alkenes are not reactive toward this process either.

Further experimental evidence was collected to gain more insights into the reaction mechanism. The catalytic amount of NaCl is quite essential for this reaction, as evidenced by a low

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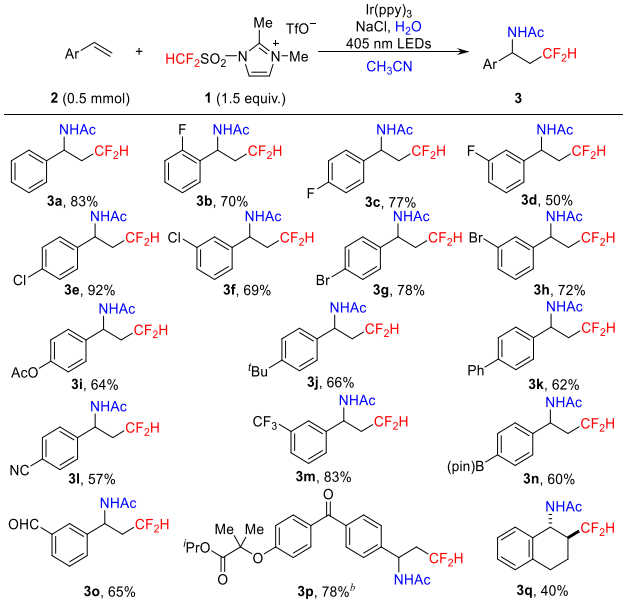
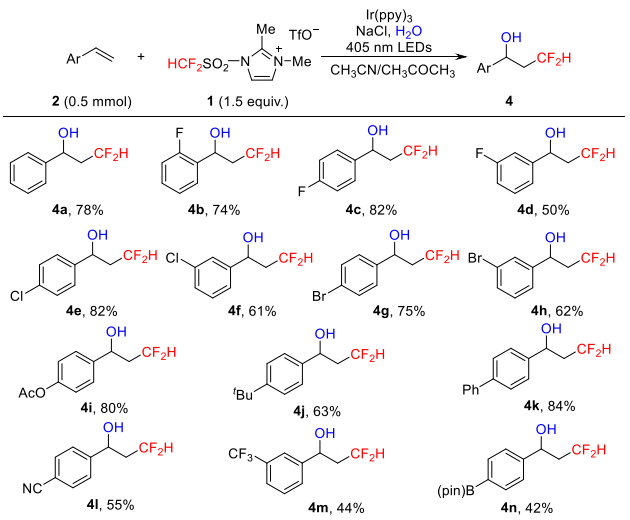
Scheme 3. Amino-difluoromethylation of Alkenes[a]



[a]Isolated yields are shown. Reaction conditions: substrate **2** (0.5 mmol), **1** (0.75 mmol), $Ir(ppy)_3$ (0.01 mmol, 2 mol %), NaCl (0.1 mmol, 20 mol %), H_2O (0.5 mmol), and CH_3CN (5 mL) at room temperature for 10 h under the irradiation of LED lights (405 nm) under a N_2 atmosphere. [b]The reaction was performed on a 5 mmol scale.

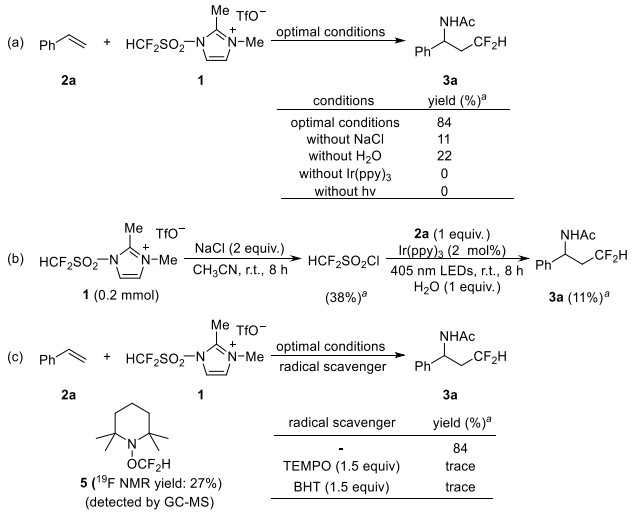
Scheme 4. Oxy-difluoromethylation of Alkenes[a]



[a]Isolated yields are shown. Reaction conditions: substrate **2** (0.5 mmol), **1** (0.75 mmol), $Ir(ppy)_3$ (0.01 mmol, 2 mol %), NaCl (0.1 mmol, 20 mol %), H_2O (0.5 mmol), CH_3CN (2.5 mL), and CH_3COCH_3 (2.5 mL) at room temperature for 10 h under the irradiation of LED lights (405 nm) under a N_2 atmosphere.

yield (11%) without it (Scheme 5a). The 1 equiv of H_2O also plays an important role, partially because it can dissolve NaCl. No desired product was detected without the photocatalyst $Ir(ppy)_3$ or without *hv*, demonstrating that the difluoromethylation reactions occur through a photoredox-catalyzed process. NaCl may act as a chloride source to convert reagent **1** into HCF_2SO_2Cl. Indeed, when 2 equiv of NaCl was used, HCF_2SO_2Cl (14% yield) was generated after the mixture of reagent **1** and NaCl had been stirred for 20 min. A hydrolysis

Scheme 5. Experimental Evidence for the Reaction Mechanism

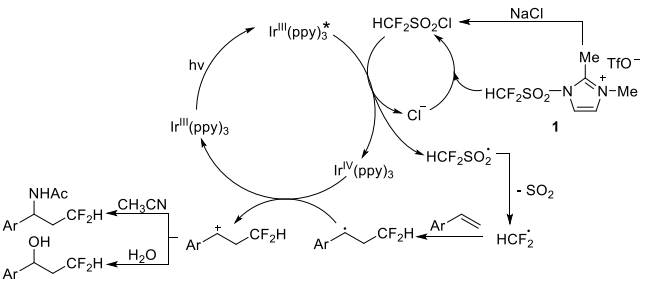


[a]The yields were determined by ^{19}F NMR spectroscopy.

side product ($HCF_2SO_3^-$) was observed, suggesting that HCF_2SO_2Cl may be quite reactive. Stirring the mixture for 8 h allowed the full conversion of reagent **1**; however, an only 38% ^{19}F NMR yield of HCF_2SO_2Cl was obtained, and it was mostly hydrolyzed (Scheme 5b). To the reaction system were added substrate **2a** and other reagents, the desired aminodifluoromethylation could still occur (Scheme 5b). The low yield of **3a** should be because of the low loading of HCF_2SO_2Cl and the water sensitivity of HCF_2SO_2Cl. If the reaction was performed by a one-step process, as shown in Schemes 3 and 4, HCF_2SO_2Cl generated in situ may readily undergo reduction rather than hydrolysis, resulting in high yields for bifunctionalization. When a radical scavenger is present, such as 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and 2,6-di-*tert*-butyl-4-methylphenol (BHT), the desired conversion was almost completely suppressed (Scheme 5c). In addition, TEMPO-CF_2H (**5**) was generated in a 27% ^{19}F NMR yield in the case of TEMPO as the radical scavenger. Apparently, a radical mechanism is operative for the difluoromethylation of alkenes.

On the basis of the results presented above, a plausible reaction mechanism is proposed in Scheme 6. A chlorine–

Scheme 6. Plausible Reaction Mechanism



imidazole exchange between reagent **1** and NaCl affords HCF_2SO_2Cl, which is then reduced by photoexcited complex [$Ir(ppy)_3$*] to provide Ir^{IV} and the $HCF_2SO_2^{\bullet}$ radical. The Cl^- anion produced in situ can further convert reagent **1** into HCF_2SO_2Cl, explaining why only a catalytic amount of NaCl is required. The $HCF_2^{\bullet}$ radical, generated from $HCF_2SO_2^{\bullet}$ by a

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facile desulfonylation, is easily captured by an aryl alkene to deliver a benzyl radical. The redox reaction between the benzyl radical and Ir^{IV} releases the Ir catalyst and furnishes a benzyl cation, which is attacked by a nucleophile to give the final product. It is still unclear why the presence of acetone leads to the oxy-difluoromethylation process.

In summary, we have designed an efficient synthetic route for the successful access to a difluoromethylsulfonyl imidazolium salt and described the use of this salt as a reagent for the amino- and oxy-difluoromethylation of alkenes. The synthesis of the imidazolium salt does not require any tedious purification procedure, and it can be easily obtained in a moderate overall yield on a large scale. Notably, the two distinct reaction paths, amino- and oxy-difluoromethylation, are determined by the reaction solvent. The use of CH_3CN and CH_3CN/CH_3COCH_3 as the solvent results in amino-difluoromethylation and oxy-difluoromethylation, respectively.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c03073.

Materials and methods, experimental procedures, and ^1H NMR, ^{19}F NMR, ^{13}C NMR, IR, and MS data (PDF)

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Notes

The authors declare no competing financial interest.

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