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Synthesis of Difluoroalkylated Arenes by Hydroaryldifluoromethylation of Alkenes with α,α-Difluoroarylacetic Acids under Photoredox Catalysis

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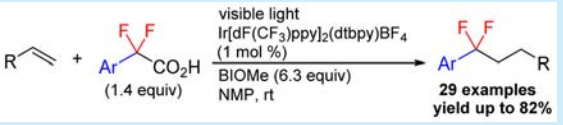
Supporting Information

ABSTRACT: A visble-light-induced hydroaryldifluoromethylation of alkenes with α,α-difluoroarylacetic acids for preparation of difluoroalkylated arenes has been developed. This reaction proceeds through the hypervalent iodine reagent promoted decarboxylation and subsequent radical hydroaryldifluoromethylation.



α,α-Difluorobenzylic compounds are an important class of aromatic motifs found in pharmaceuticals[1] because the introduction of a difluoromethylene group onto the aromatic rings can dramatically improve the metabolic stability and oral bioavailability of the parent compounds.[2] Moreover, the difluoromethylene moiety can functionalize as a bioisostere of the oxygen atom or a carbonyl group.[3] As a distinct type of α,α-difluorobenzylic compounds, difluoroalkylated arenes are present in some bioactive compounds, such as inhibitors of D-amino acid oxidase[4a] and potent antiviral agents against HIV[4b] (Figure 1).

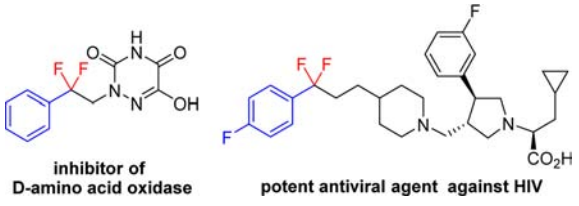
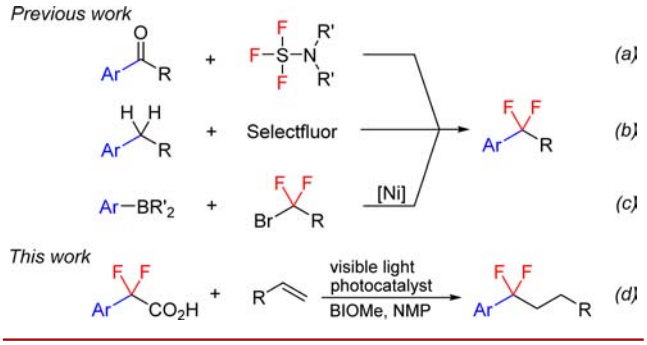


Figure 1. Bioactive compounds containing difluoroalkyl arene moieties.

Traditionally, difluoroalkylated arenes are prepared by deoxygenative fluorination of ketones with (diethylamino) sulfur trifluoride (DAST) or related aminosulfur trifluorides (Scheme 1a).[5] However, this method suffers from functional group incompatibility and the use of toxic fluorinating reagents. Recently, impressive breakthroughs in the construction of difluoroalkylated arenes have been achieved by direct fluorination of benzylic C−H bonds (Scheme 1b)[6] and nickel-catalyzed difluoroalkylation of arylboron reagents (Scheme 1c).[7] Despite the this progress, the efficient approaches to difluoroalkylated arenes are still limited.

α,α-Difluoroarylacetic acids are stable and easily accessible building blocks for the preparation of fluorinated compounds.

Scheme 1. Synthetic Methods ToAchieve Difluoroalkylated Arenes



For example, the decarboxylative functionalization of α,α-difluoroarylacetic acids has been applied for the synthesis of difluoromethylated arenes,[8a] trifluoromethylated arenes,[8b] aryldifluoromethylated alkynes,[8c,d] and aryldifluoromethylated phenanthridines.[8e] However, the preparation of aryldifluoromethylated alkanes using α,α-difluoroarylacetic acids has not been reported yet. Very recently, our group has prepared a series of fluoroalkylated alkanes by hydrotrifluoromethylation,[9a] hydrobromodifluoromethylation,[9b] hydrodifluoromethylation,[9c] and hydrocarbomethoxydifluoromethylation[9d] of alkenes with different fluoroalkylating reagents. Herein, we disclose the photoredox-catalyzed hydroaryldifluoromethylation of alkenes with α,α-difluoroarylacetic acids to difluoroalkylated arenes (Scheme 1d).

Recently, visible-light photoredox catalysis has emerged as a mild and powerful method in organic synthesis.[10] The application of this strategy to decarboxylative functionalization of carboxylic acids has received increasing attention.[10f] To

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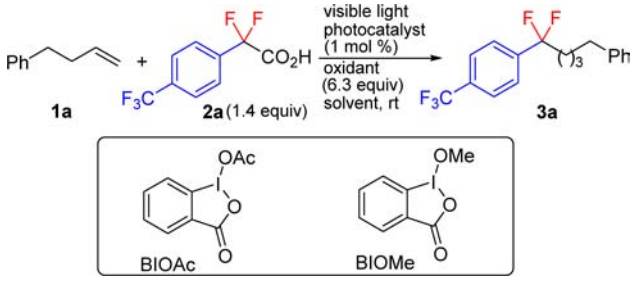
extend the scope of visible-light-promoted decarboxylation reactions, we were interested in the decarboxylative functionalization of α,α-difluoroarylacetic acids with alkenes for synthesis of difluoroalkylated arenes. Initially, the decarboxylation of the model substrate, 2,2-difluoro-2-(4-(trifluoromethyl)phenyl)acetic acid (**2a**), in the presence of common photocatalysts including $Ru(bpy)_3(PF_6)_2$, *fac*-$Ir(ppy)_3$, and eosin Y was investigated. To our disappointment, the decarboxylative reaction did not take place. Inspired by the elegant work of decarboxylative functionalization of carboxylic acids promoted by hypervalent iodine reagents (HIRs),[11] the hydroaryldifluoromethylation of 4-phenyl-1-butene (**1a**) with **2a** by combining the photocatalyst and $PhI(OAc)_2$ in NMP was then explored. As we expected, the hydroaryldifluoromethylated product **3a** was formed, albeit in low yields (Table 1, entries 1−3). Further examination of different photocatalysts showed that $Ir(dtbbpy)(ppy)_2PF_6$ and $Ir[dF(CF_3)ppy]_2(dtbpy)BF_4$[12] gave higher yields (entries 4 and 5). Switching $PhI(OAc)_2$ to other HIRs including $PhI(OCOCF_3)_2$, acetoxybenziodoxole (BIOAc), and methoxybenziodoxole (BIOMe) also promoted this reaction (entries 6−8). Among them, BIOMe was most effective. In contrast, a typical oxidant, $K_2S_2O_8$, did not allow the desired transformation (entry 9), which revealed that BIOMe probably acts not only as an oxidant but also as an activating reagent.[11c−e,g] When the reaction was performed in DMF, THF, DMAc (*N*,*N*-dimethylacetamide), or MeOH, lower yields were obtained (entries 10−13). Furthermore, the addition of hydrogen sources, including diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (Hantzsch ester), 1,4-cyclohexadiene (1,4-CHD), Et_3SiH, or MeOH, also led to lower yields (entries 14−17). Finally, a study of reaction concentrations showed that a 0.067 M concentration of **1a** in NMP gave the highest yield (entries 18 and 19). It was noteworthy that the control experiments confirmed that BIOMe, photocatalyst, and light irradiation were all critical for this reaction (entries 20−22).

With the optimized conditions in hand, we first explored the scope with respect to alkenes (Scheme 2). A number of alkenes (**1a−r**) underwent hydroaryldifluoromethylation to afford the corresponding products (**3a−r**) in moderate to high yields. Functional groups such as alkyl bromide, alcohol, ether, epoxy, aldehyde, ketone, ester, phosphate, amide, and nitrile were well tolerated (**1c−m**). The α,β-unsaturated sulfone **1n** exhibited a high reactivity. In the cases of acrylates, the desired products were obtained in low yields. Moreover, geminally disubstituted alkene **1o** was also compatible with the reaction conditions. Unfortunately, 1,2-disubstituted alkenes and styrenes were not viable for this protocol. The substrates **1p−r** bearing aryl halides or tosylate were also transformed to the corresponding products **3p−r**.

We then examined the scope with regard to α,α-difluoroarylacetic acids (Scheme 3). Various α,α-difluoroarylacetic acids **2** bearing either electron-donating or electron-withdrawing groups at different positions of the phenyl ring reacted with alkenes efficiently. In general, α,β-unsaturated sulfone gave higher yields (**3ae−ak**) than the unactivated alkenes (**3aa−ad**). Notably, 2,2-difluoro-2-(thiophene-2-yl)acetic acid was also effective in this reaction (**3ak**).

To gain more insight into the reaction mechanism, the following experiments were carried out. When the radical quencher 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) was added to the optimized reaction conditions of **1n** and **2a**, none of the desired product **3n** was detected (Scheme 4a). This result indicates that a radical process is probably involved. We also carried out the isotopic labeling experiment with DMF-d_7 as the solvent (Scheme 4b). The exclusive formation of the deuterated product [**D**]**3n** unambiguously confirms that the hydrogen atom arises from the solvent. Furthermore, as mentioned in entry 20 of Table 1, the reaction of **1a** and **2a** in the absence of BIOMe could not give the desired product. In contrast, the reaction of **1a** and an $ArCF_2$-containing HIR **4** with or without $PhI(OAc)_2$ afforded **3ab** in moderate yields

Table 1. Optimization of Reaction Conditions[a]



entry	photocatalyst	oxidant	solvent	yield[b] (%)
1	$Ru(bpy)_3(PF_6)_2$	$PhI(OAc)_2$	NMP	24
2	*fac*-$Ir(ppy)_3$	$PhI(OAc)_2$	NMP	29
3	Eosin Y	$PhI(OAc)_2$	NMP	36
4	$Ir(dtbbpy)(ppy)_2PF_6$	$PhI(OAc)_2$	NMP	41
5	$Ir[dF(CF_3)ppy]_2(dtbpy)BF_4$	$PhI(OAc)_2$	NMP	48
6	$Ir[dF(CF_3)ppy]_2(dtbpy)BF_4$	$PhI(OCOCF_3)_2$	NMP	8
7	$Ir[dF(CF_3)ppy]_2(dtbpy)BF_4$	BIOAc	NMP	46
8	$Ir[dF(CF_3)ppy]_2(dtbpy)BF_4$	BIOMe	NMP	61
9	$Ir[dF(CF_3)ppy]_2(dtbpy)BF_4$	$K_2S_2O_8$	NMP	0
10	$Ir[dF(CF_3)ppy]_2(dtbpy)BF_4$	BIOMe	DMF	24
11	$Ir[dF(CF_3)ppy]_2(dtbpy)BF_4$	BIOMe	THF	34
12	$Ir[dF(CF_3)ppy]_2(dtbpy)BF_4$	BIOMe	DMAc	28
13	$Ir[dF(CF_3)ppy]_2(dtbpy)BF_4$	BIOMe	MeOH	3
14[c]	$Ir[dF(CF_3)ppy]_2(dtbpy)BF_4$	BIOMe	NMP	21
15[d]	$Ir[dF(CF_3)ppy]_2(dtbpy)BF_4$	BIOMe	NMP	22
16[e]	$Ir[dF(CF_3)ppy]_2(dtbpy)BF_4$	BIOMe	NMP	45
17[f]	$Ir[dF(CF_3)ppy]_2(dtbpy)BF_4$	BIOMe	NMP	55
18[g]	$Ir[dF(CF_3)ppy]_2(dtbpy)BF_4$	BIOMe	NMP	74
19[h]	$Ir[dF(CF_3)ppy]_2(dtbpy)BF_4$	BIOMe	NMP	68
20[g]	$Ir[dF(CF_3)ppy]_2(dtbpy)BF_4$		NMP	0
21[g]		BIOMe	NMP	trace
22[g,i]	$Ir[dF(CF_3)ppy]_2(dtbpy)BF_4$	BIOMe	NMP	0

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.14 mmol), photocatalyst (0.001 mmol), oxidant (0.63 mmol), solvent (1.0 mL), visible light, rt, under N_2, 10 h. [b]Yields determined by ^{19}F NMR spectroscopy using trifluoromethylbenzene as an internal standard. [c]Hautzsch ester (0.15 mmol). [d]1,4-CHD (0.15 mmol). [e]Et_3SiH (0.15 mmol). [f]MeOH (0.15 mmol). [g]NMP (1.5 mL). [h]NMP (2.0 mL). [i]No light.

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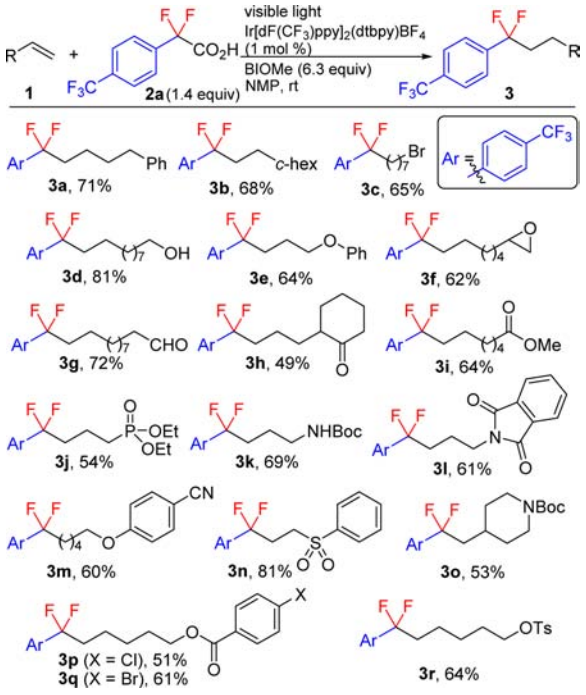
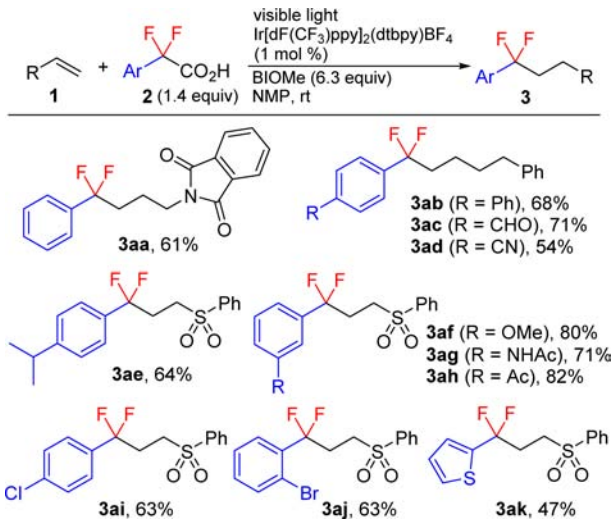
Scheme 2. Scope of Alkenes[a]



[a]Reaction conditions: **1** (0.3 mmol), **2a** (0.42 mmol), Ir[dF(CF_3)ppy]$_2$(dtbpy)BF_4 (0.003 mmol), BIOMe (1.89 mmol), NMP (4.5 mL), visible light, rt, under N_2, 10 h, isolated yields.

Scheme 3. Scope of α,α-Difluoroarylacetic Acids[a]

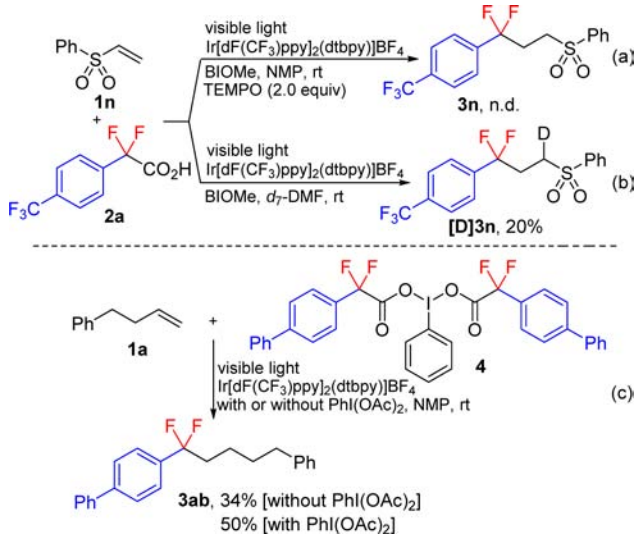


[a]Reaction conditions: **1** (0.3 mmol), **2** (0.42 mmol), Ir[dF(CF_3)ppy]$_2$(dtbpy)BF_4 (0.003 mmol), BIOMe (1.89 mmol), NMP (4.5 mL), visible light, rt, under N_2, 10 h, isolated yields.

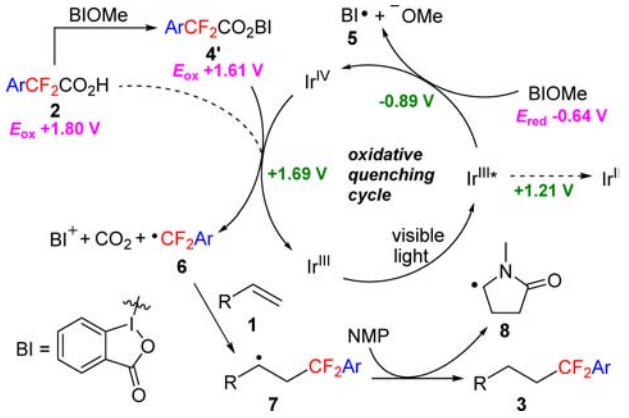
(Scheme 4c), which implied that $ArCF_2$-containing HIR may be an important intermediate involved in the reaction.

On the basis of the above experimental results as well as previously reported work,[11a,c−e,g] a possible mechanism for the reaction is proposed in Scheme 5. First, irradiation of Ir^{III} with visible light generates its excited-state Ir^{III}*. At the same time, α,α-difluoroarylacetic acid **2** reacts with BIOMe to form $ArCF_2$-containing HIR **4′**. The excited-state Ir^{III}* might either be oxidized to Ir^{IV} [$E_{1/2}$ (Ir^{III}*/Ir^{IV}) = −0.89 V vs SCE in CH_3CN] or reduced to Ir^{II} [$E_{1/2}$ (Ir^{III}*/Ir^{II}) = +1.21 V vs SCE in

Scheme 4. Mechanistic Investigations



Scheme 5. Proposed Reaction Mechanism



CH_3CN].[12] In consideration of the oxidation/reduction potentials of **2**, **4′**, and BIOMe (see the Supporting Information), the single-electron transfer (SET) reduction of BIOMe (−0.64 V vs SCE in CH_3CN) is concurrent with the oxidation of Ir^{III}* to Ir^{IV},[11a,13] and the SET oxidation of **2** (+1.80 V vs SCE in CH_3CN) or **4′** (+1.61 V vs SCE in CH_3CN)[14] by Ir^{III}* is thermodynamically unfeasible. Consequently, the current reaction occurs through an oxidative quenching cycle. Then the SET oxidation of **4′** by Ir^{IV} generates aryldifluoromethyl radical **6**. It was noteworthy that difluoroarylacetic acid **2** was not directly oxidized by Ir^{IV} [$E_{1/2}$ (Ir^{IV}/Ir^{III}) = +1.69 V vs SCE in CH_3CN][12] to generate aryldifluoromethyl radical **6**.[15] Subsequently, the addition of radical **6** to alkene **1** affords radical intermediate **7**, which abstracts hydrogen from NMP to give the hydroaryldifluoromethylated product **3**.[16] As shown in Scheme 5, BIOMe was used not only as oxidant for transformation of Ir^{III}* into Ir^{IV} but also as promoter for the decarboxylation. That is why the excess of BIOMe was required for the formation of the products in high yield.

In conclusion, we have developed a new synthetic method of difluoroalkylated arenes using the stable and easily accessible α,α-difluoroarylacetic acids under photoredox catalysis. The HIR, BIOMe, was found to be crucial for this decarboxylative aryldifluoromethylation reaction. This protocol is tolerant of

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various functional groups, which makes it attractive for the preparation of aryldifluoromethylated compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03092.

Experimental procedures, characterization data, and ^{1}H, ^{19}F, and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(14) The separation of pure $ArCF_2$-containing HIR **4′** is difficult. Thus, we measured the first oxidation potential of **4** instead.

(15) This could be the reason why the decarboxylation of **2a** in the absence of HIR did not occur (Table 1, entry 20).

(16) The further transformations of radical intermediates **5** and **8** are still unclear and remain to be elucidated.

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