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Visible light promoted carbodifluoroalkylation of allylic alcohols *via* concomitant 1,2-aryl migration†

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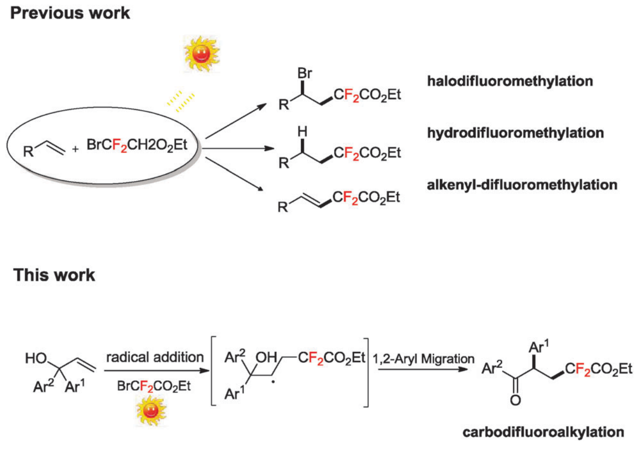
A novel visible light promoted carbodifluoroalkylation of allylic alcohols is disclosed. A series of difluoro 1,5-dicarbonyl compounds were obtained through a tandem radical addition and 1,2-aryl migration process. Mechanistic analysis indicated that the 1,2-aryl rearrangement proceeded *via* a radical intermediate.

The introduction of fluorinated functional groups into organic molecules is becoming a hot topic as organofluorine compounds are of great interest in pharmaceutical, agricultural, and functional materials.[1] Over the past few decades, substantial efforts have been devoted to the development of new synthetic methods for fluorination[2] and trifluoromethylation[3] of target molecules. In contrast, efficient and practical difluoroalkylation methods remain limited.[4,5] In particular, the difluoroalkylation reaction is highly significant not only because incorporation of the CF_2 group may improve the molecule properties such as electronegativity, hydrophobicity, metabolic stability, and bioavailability, but also appended alkyl groups (*e.g.* CF_2CO_2Et moiety) introduce high possibility of postfunctionalization.

Visible light photoredox catalysis has received widespread attention as a powerful tool for synthetic organic chemists.[6] Seminal studies by Stephenson demonstrated that activated haloalkane ($BrCF_2CO_2Et$) could serve as a CF_2 radical precursor under visible light photoredox catalytic conditions.[7a,b] This finding provided a new way for the halodifluoromethylation of alkenes, and later several important studies about the visible light promoted difluoroalkylation reactions were reported.[7] Recently, Cho group also realized the hydrodifluoromethylation and alkenyl-difluoromethylation of alkenes.[7g] However, to the best of our knowledge, difunctionalization of alkenes involving tandem Csp^3–CF_2 and carbon–carbon bond formation has not been reported. In continuation of our interests in visible light promoted difunctionalization of alkenes,[8] we disclose our recent study about the visible light promoted carbodifluoroalkylation of allylic alcohols through a tandem difluoroalkylation/1,2-aryl migration process (Scheme 1).[9]

Initial investigation of the reaction parameters was conducted using $Ir(ppy)_3$ as the photoredox catalyst and KOAc as the base (see Table 1, also the ESI†). When a solution of allylic alcohol **1a** and $BrCF_2CO_2Et$ in CH_3CN was irradiated by 5W Blue LED light (light-emitting diode strips, λ_{max} = 455 nm) in the catalysis of $Ir(ppy)_3$, our proposed sequential difluoroalkylation/1,2-aryl migration process could occur with a satisfactory yield of 69% (entry 1). Excess $BrCF_2CO_2Et$ is necessary for the full conversion of allylic alcohol. With this encouraging result, further screening about the influence of solvent, catalyst and base was investigated respectively. Firstly, different solvents were tested (entries 2–5). It was found that a transesterification process of the target product would occur when CH_3OH was used as solvent (entry 4). Among the solvents tried, DMF showed best efficiency as a delightful yield of 83% could be obtained (entry 5). The replacement of $Ir(ppy)_3$ with other photoredox



Scheme 1 difluoroalkylation reactions of alkenes.

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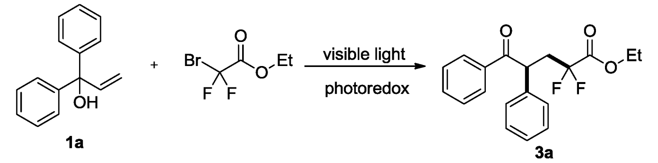
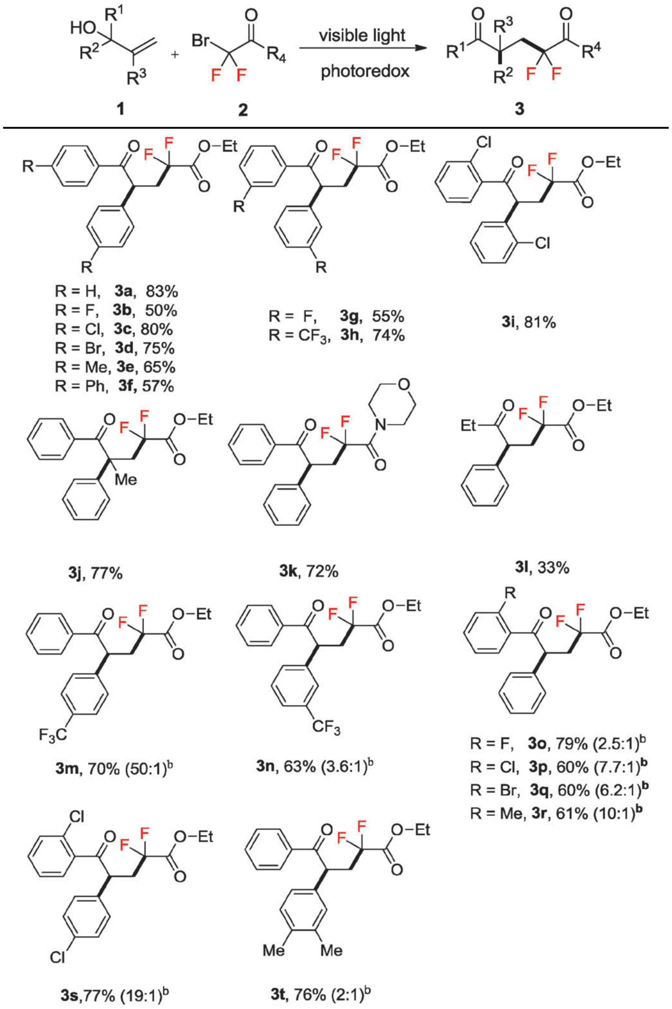
Table 1 Optimization of reaction conditions[a]



Entry	Photocatalyst	Base	Solvent	Yield[b] (%)
1	*fac*-Ir(ppy)$_3$	KOAc	CH_3CN	69
2	*fac*-Ir(ppy)$_3$	KOAc	DCM	50
3	*fac*-Ir(ppy)$_3$	KOAc	DMSO	55
4	*fac*-Ir(ppy)$_3$	KOAc	CH_3OH	53[c]
5	***fac*-Ir(ppy)$_3$**	**KOAc**	**DMF**	**83**
6	Ir(ppy)$_2$(dtbpy)PF$_6$	KOAc	DMF	69
7	Ru(bpy)$_3$(PF$_6$)$_2$	KOAc	DMF	37
8	*fac*-Ir(ppy)$_3$	—	DMF	0
9	*fac*-Ir(ppy)$_3$	NaOAc	DMF	76
10	*fac*-Ir(ppy)$_3$	$NaHCO_3$	DMF	71
11	*fac*-Ir(ppy)$_3$	K_2HPO_4	DMF	56
12	*fac*-Ir(ppy)$_3$	Na_2HPO_4	DMF	38
13	*fac*-Ir(ppy)$_3$	K_2CO_3	DMF	53
14	—	KOAc	DMF	0
15[d]	*fac*-Ir(ppy)$_3$	KOAc	DMF	0

[a] Reaction conditions: **1a** (0.2 mmol), $BrCF_2CO_2Et$ (0.5 mmol), Base (0.3 mmol), photocatalyst (2 mol%), solvent (1 mL), 5W Blue LED light, 24 h, rt. [b] Isolated yield. [c] CF_2CO_2Me substituted product was formed. [d] In the dark.

Table 2 Scope of carbodifluoroalkylation of allylic alcohols[a]



[a] The reactions were carried out with **1** (0.2 mmol), **2** (0.5 mmol), potassium acetate (0.3 mmol), and *fac*-Ir(ppy)$_3$ (2 mol%) in DMF (1 mL) at room temperature, 5W Blue LEDs, 24–40 h. [b] The ratio of **3** to its isomer was determined by ^1H NMR analysis of the crude product.

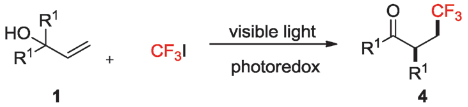
catalysts such as Ir(ppy)$_2$(dtbpy)PF$_6$ or Ru(bpy)$_3$(PF$_6$)$_2$ resulted in lower yields of this transformantion (entries 6 and 7). The choice of base is vital to this reaction. Particularly, this reaction was absolutely prevented when no base was added in the reaction system (entry 8). This noticeable influence of base prompted us to screen more bases (entries 9–12). The results indicated that KOAc could promote the reaction with the best yield (entry 5). The control experiment showed that the reaction could not proceed in the absence of a photoredox catalyst and visible light (entries 14 and 15).

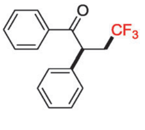
With optimized reaction conditions in hand (Table 1, entry 5), we investigated the scope of this visible-light promoted carbodifluoroalkylation with a range of α,α-diaryl allylic alcohols (Table 2). Various allylic alcohols with electron-withdrawing or electron-donating aryl groups furnished the corresponding migration products with moderate to good yields (**3a–3f**). It was found that the position of substitutes on the aromatic ring has no considerable effect on the reaction (**3g–3i**). Difluoro substituted ketone **3j** which contains an α-quaternary center was also obtained with a good yield. Considering the typical biological activities of molecules containing a difluoroacetamide fragment, bromodifluoroacetamide **2k** was studied as a difluorinating reagent. The tandem carbodifluoroalkylation of allyic alcohol **1a** with bromodifluoroacetamide proceeded well, giving the desired product in a good yield (**3k**). Remarkably, when α-aryl-α-alkyl-substituted allyic alcohol was tried, only the product with aryl group migration was detected in a low yield (**3l**). Next, unsymmetrical allylic alcohols were investigated to get a more deep understanding of the migration process. The rearrangement process preferentially occurred on the aryl ring bearing an electron deficient group (**3m–3n**). This phenomenon indicates that this visible light promoted concomitant 1,2-aryl migration occurs *via* a radical other than a cationic intermediate,[10] and it is different from the classic semipinacol rearrangements.[11] On the other hand, the sterical hindrance effect is also an important factor that *ortho*-substituted aromatic rings migrated less effectively (**3o–3r**). A similar rule is suitable for substrate **1s** with a *p*-Cl–Ph group and a *o*-Cl–Ph group. In addition, **3t** was obtained as the major product, abeit with a low chemoselectivity (2 : 1). It is worth mentioning that no epoxide products were detected in all above examples.

Although trifluoromethylation-induced 1,2-aryl rearrangement has been realized through Cu or Fe catalysis with a Togni reagent,[9c,d] a visible light photoredox protocol using commercially available and relatively inexpensive reagent CF_3I as the CF_3 source is still valueable.[12] As shown in Table 3, various β-trifluoromethyl α-aryl ketones could be obtained in moderate to good yields under similar conditions using Ru(bpy)$_3$(PF$_6$)$_2$ as the catalyst.[13]

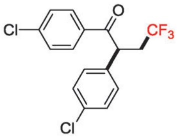
To get an insight of the mechanism of this transformation, a radical-trapping experiment was carried out. It was found that

Table 3 Examples of carbotrifluoroalkylation of allylic alcohols[a]

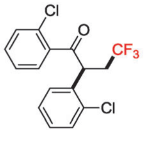




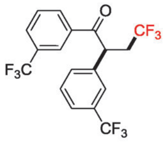
4a, 60%



4b, 80%



4c, 90%

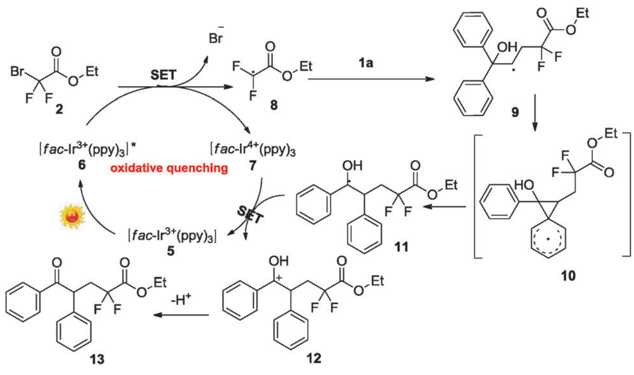


4d, 81%

[a] The reactions were carried out with **1** (0.2 mmol), CF_3I (1 mmol), potassium acetate (0.3 mmol), and $Ru(bpy)_3(PF_6)_2$ (2 mol%) in DMF (1 mL) at room temperature, 5W blue LEDs, 24–30 h.

no product was detected in the presence of a radical inhibitor TEMPO, which further implies a single electron transfer (SET) process. Based on this result, a possible mechanism is proposed. Firstly, a photoredox catalyst *fac*-$Ir^{3+}(ppy)_3$ undergoes a metal to ligand charge transfer (MLCT) process by visible light to produce the excited state Ir^{3+}* **6**. A SET process then occurs between **6** and ethyl 2-bromo-2,2-difluoroacetate **2** with the generation of Ir^{4+} **7** and CF_2 radical precursor **8**. Subsequently, active radical **8** will react with **1a** to generate intermediate **9**, which soon undergoes 1,2-aryl migration *via* key spiro[2.5]octadienyl radical **10**. Ultimately the generated intermediate **11** is oxidized to the corresponding carbocation **12** through single-electron oxidation. Further deprotonation of **12** will give product **13**. As we mentioned in the substrate expansion, a mechanism involving 'neophyl'[10] rearrangement is more likely than semipinacol rearrangement. Therefore, a process in which single-electron oxidation occurs ahead of 1,2-aryl migration may be ruled out (Scheme 2).

In summary, we have developed the first carbodifluoroalkylation of allylic alcohols through visible light promoted radical 1,2-aryl migration. It provides an efficient method for the synthesis of functionalized difluoro 1,5-dicarbonyl compounds. Besides, we also provide a new and efficient method for the synthesis of β-trifluoromethyl α-aryl ketones. Further explorations about intermolecular carbodifluoroalkylation are under way in our lab.



Scheme 2 Proposed mechanism.

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13 For brief optimization of the catalyst for carbotrifluoromethylation, please see ESI†.