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COMMUNICATION

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

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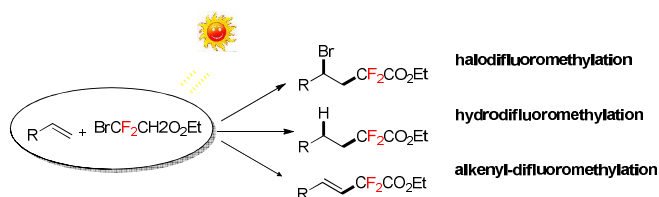
A novel visible light promoted carbodifluoroalkylation of allylic alcohols is disclosed. A series of difluoro 1,5-dicarbonyl compounds were obtained through a tandem radical addition and 1,2-aryl migration. Mechanistic analysis indicated the 1,2-aryl rearrangement proceeded via a radical intermediate.

The introduction of fluorinated functional groups into organic molecules has becoming a hot topic as organofluorine compounds are of great interests in pharmaceutical, agricultural, and functional materials.^[1] Over the past decades, substantial efforts have been devoted to developing 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 CF₂ group may improve the molecules properties such as electronegativity, hydrophobicity, metabolic stability, and bioavailability, but also appended alkyl groups (e.g. CF₂CO₂Et moiety) introduce huge possibility of postfunctionalization.

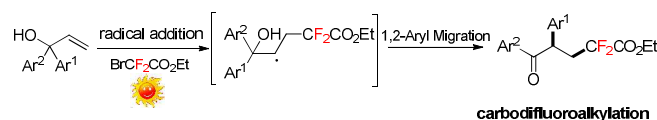
Visible light photoredox catalysis has received widespread attention as a powerful tool for synthetic organic chemists.^[6] Seminal works by Stephenson demonstrated activated haloalkane (BrCF₂CO₂Et) could serve as CF₂ radical precursor under visible light photoredox catalytic condition.^[7a,b] This finding provided a new way for the halodifluoromethylation of alkenes, and later several important works 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 Csp³-CF₂ and carbon carbon bond formation have 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 tandem difluoroalkylation/1,2-aryl migration process.^[9]

Initial investigation of the reaction parameters was conducted using Ir(ppy)₃ as photoredox catalyst and KOAc as base (see Table 1, also the supporting information). When a solution of allylic alcohol **1a** and BrCF₂CO₂Et in CH₃CN was irradiated by 5W Blue LED

Previous work

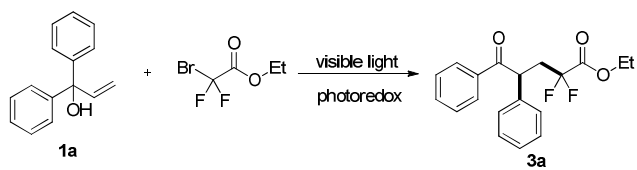


This work



Scheme 1 difluoroalkylation reactions of alkenes.

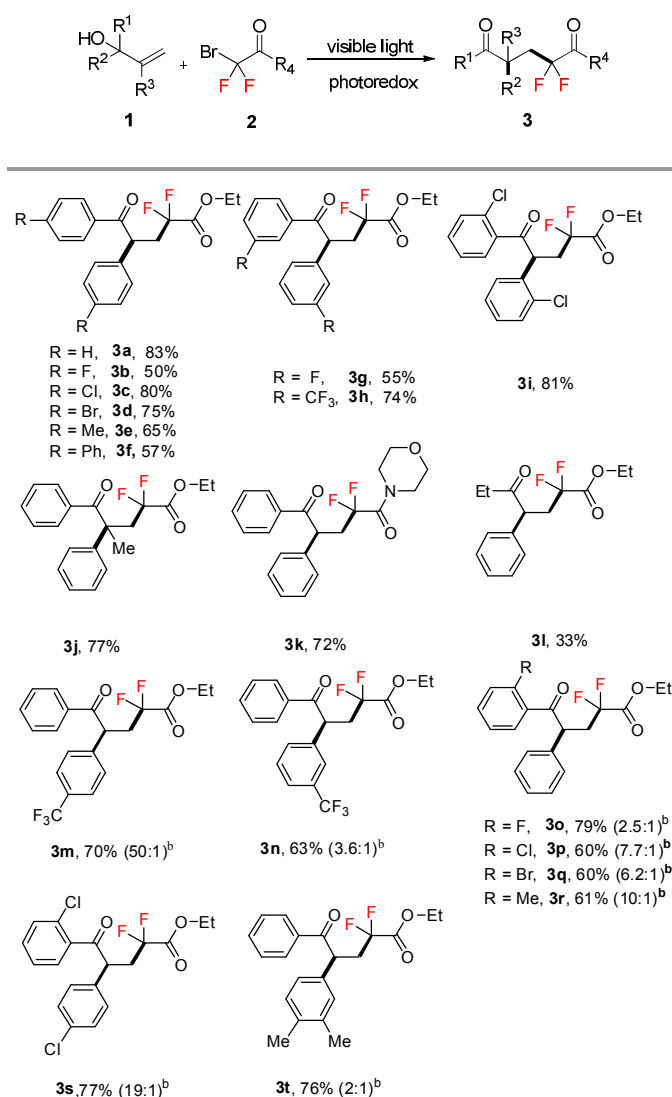
light (light-emitting diode strips, $\lambda_{\max} = 455$ nm) in the catalysis of Ir(ppy)₃, our proposed sequential difluoroalkylation/1,2-aryl migration process could occur with a satisfactory yield of 69% (entry 1). Excess BrCF₂CO₂Et is necessary of the full conversion of allylic alcohol. With this encouraging result, further screening about the influence of solvent, catalyst and base were investigated respectively. Firstly, different solvents were tested (entry 2-5). It was found that a transesterification process of target product would happen when CH₃OH 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 catalysts such as Ir(ppy)₂(dtbpy)PF₆ or Ru(bpy)₃(PF₆)₂ resulted in lower yields of this transformation (entry 6 and 7). 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 (entry 9-12). The results indicated KOAc could promoted the reaction with the best yield (entry 5). The control experiment showed the reaction could not proceed in the absence of photoredox catalyst and visible light (entry 14 and 15).

Table 1 Optimization of reaction conditions^a


Entry	photocatalyst	Base	solvent	Yield(%) ^b
1	<i>fac</i> -Ir(ppy) ₃	KOAc	CH ₃ CN	69
2	<i>fac</i> -Ir(ppy) ₃	KOAc	DCM	50
3	<i>fac</i> -Ir(ppy) ₃	KOAc	DMSO	55
4	<i>fac</i> -Ir(ppy) ₃	KOAc	CH ₃ OH	53 ^c
5	<i>fac</i>-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	<i>fac</i> -Ir(ppy) ₃	-	DMF	0
9	<i>fac</i> -Ir(ppy) ₃	NaOAc	DMF	76
10	<i>fac</i> -Ir(ppy) ₃	NaHCO ₃	DMF	71
11	<i>fac</i> -Ir(ppy) ₃	K ₂ HPO ₄	DMF	56
12	<i>fac</i> -Ir(ppy) ₃	Na ₂ HPO ₄	DMF	38
13	<i>fac</i> -Ir(ppy) ₃	K ₂ CO ₃	DMF	53
14	-	KOAc	DMF	0
15 ^d	<i>fac</i> -Ir(ppy) ₃	KOAc	DMF	0

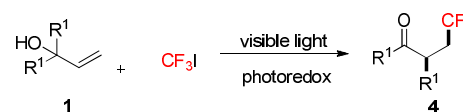
a Reaction conditions: **1a** (0.2 mmol), BrCF₂CO₂Et (0.5 mmol), Base (0.3 mmol), photocatalyst (2 mol%), solvent (1 mL), 5 W Blue LED light, 24 h, rt. ^b Isolated yield. ^c CF₂CO₂Me substituted product was formed. ^d In the dark.

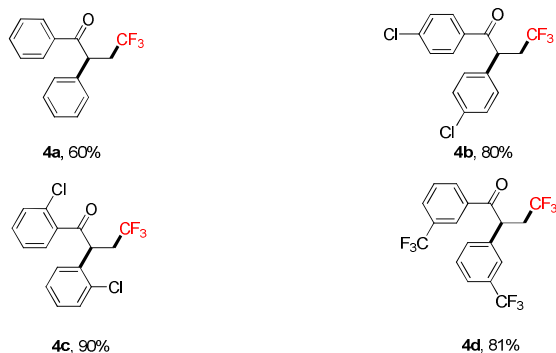
With optimized reaction conditions in hand (Table 1, entry 5), we investigated the scope of this visible-light promoted carbodifluoroalkylation with a range of α,α -diaryl allylic alcohols (Table 2). Various allylic alcohols with electron-withdrawing or electron-donating aryl groups furnished corresponding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

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.

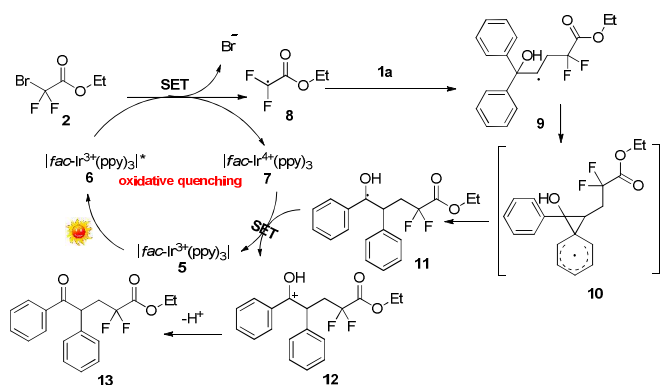
Although trifluoromethylation-induced 1,2-aryl rearrangement has been realized through Cu or Fe catalysis with Togni reagent^[9c,d], a visible light photoredox protocol using commercially available and relatively inexpensive reagent CF₃I as CF₃ source is still valuable.^[12] As shown in Table 3, various β -trifluoromethyl α -aryl ketones could be obtained in moderate to good yields under a similar condition using Ru(bpy)₃(PF₆)₂ as catalyst.^[13]

Table 3 Examples of carbotrifluoroalkylation of allylic alcohols^a



^a The reactions were carried out with **1** (0.2 mmol), CF₃I (1 mmol), potassium acetate (0.3 mmol), and Ru(bpy)₃(PF₆)₂ (2 mol%) in DMF (1 mL) at room temperature, 5w blue LEDs, 24-30 h.

To get an insight of mechanism of this transformation, a radical-trapping experiment was carried out. It was found that no product was detected in the presence of radical inhibitor TEMPO, which further implies a single electron transfer (SET) process. Based on this result, a possible mechanism is proposed. Firstly, photoredox catalyst *fac*-Ir³⁺(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 happens between **6** and ethyl 2-bromo-2,2-difluoroacetate **2** with the generation of Ir⁴⁺ **7** and CF₂ 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 a single-electron oxidation. Further deprotonation of **12** will give the product **13**. As we mentioned in the substrate expansion, a mechanism involved ‘neophyl’^[10] rearrangement is more likely than semipinacol rearrangement. Therefore, a process that single-electron oxidation happens ahead of 1,2-aryl migration may be ruled out.



Scheme 2 Proposed mechanism.

Conclusions

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.

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Notes and references

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