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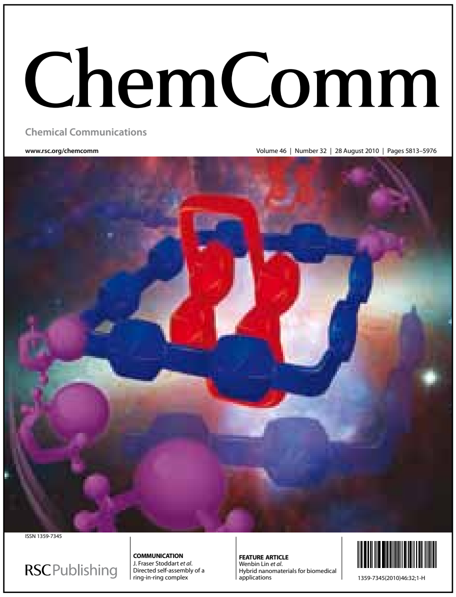

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Room Temperature Decarboxylative Trifluoromethylation of *α,β*-Unsaturated Carboxylic Acids by Photoredox Catalysis

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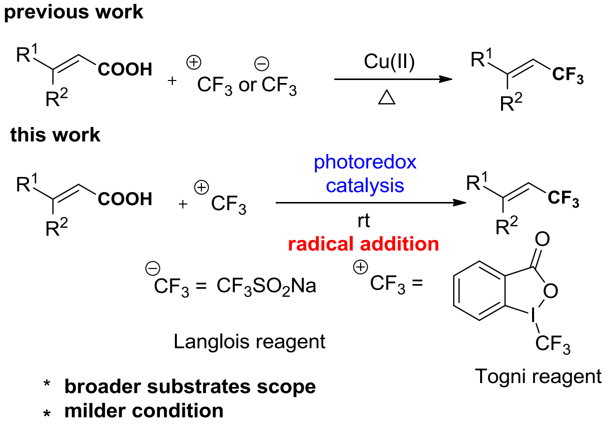
A visible-light-induced decarboxylative trifluoromethylation of *α,β*-unsaturated carboxylic acids that uses the Togni reagent as the CF_3 source is disclosed. The corresponding trifluoromethylated alkenes were obtained in moderate to high yields with excellent functional group tolerance at ambient temperature. Preliminary mechanistic analyses suggest a radical-type mechanism.

The introduction of CF_3 group in a target molecule has served as a feasible strategy for the optimization of drug candidates, agrochemicals, and functional materials, because organofluorine compounds possess unique physical properties and biological activities. [1,2] Over the past several years, extensive efforts have been made toward the development of approaches for introducing trifluoromethyl groups into arenes. [3,5] However, only a few examples of constructing C_{vinyl}-CF_3 bonds were reported while trifluoromethylated alkenes are also significant intermediates or end products (e.g. bifenthrin). [4,5]

Transition-metal-catalyzed trifluoromethylations of vinylboronic acids to synthesise trifluoromethylated alkenes have independently been realized by Liu,[5a] Shen,[5b] Buchwald,[4a,4b] and Akita.[4c] In 2012, considering the difficult preparations of vinylboronic acids and its derivatives, Hu reported the copper-catalyzed decarboxylative trifluoromethylation of commercially available *α,β*-unsaturated carboxylic acids with Togni reagent.[4d] Recently, liu improved the method with a cheaper Langlois reagent.[4e] Most these methods, howere, suffer from several disadvantages, such as harsh conditions with relatively high temperature, or limited substrate scopes. Accordingly, a new efficient method for constructing C_{vinyl}-CF_3 bonds bearing broad scope under mild reaction condition is desired. In continuation of our interest in photoredox catalysis[6,7] and our recently disclosed studies on the visible-light-promoted tandem carbotrifluoromethylation[6c] and decarboxylative alkylation reactions,[6d] we focus our attention on directly decarboxylative trifluoromethylation of *α,β*-unsaturated carboxylic acids by photoredox catalysis.

We initially chose *fac*-Ir(ppy)$_3$ as photocatalyst for the screening of the transformation. When a solution of acrylic acid **1a** and air-stable Togni reagent[8] in DMF was irradiated by 35W fluorescent light bulb in the catalysis of *fac*-Ir(ppy)$_3$, the decarboxylative trifluoromethylation reaction could occur with a low yield of 30% (Table 1, entry 1).

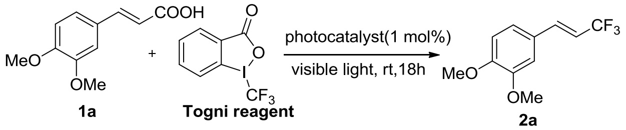


Scheme 1 Trifluoromethylation of *α,β*-Unsaturated Carboxylic Acids.

With this delightful initial result, we further optimized the reaction conditions in detail (see Table 1, also the Supporting Information). Firsty, different solvents were tested and it was found that a satisfactory yield of 65% could be obtained when DMSO was used (entries 2-4). The choice of photocatalyst was vital to this reaction for other catalysts show distinctly low effiency (entries 5-7). To maximize the yields of this decarboxylative reaction, we tried to add some acids or bases in the reaction system (entries 8-12). However, when EtONa was used, the yield was somewhat decreased (entry 8). What's more, additives like NaOH and TsOH absolutely prevented the reaction (entries 9 and 10). Considering the noticeable impact of additives, more bases were screened (entries 11 and 12). The results indicated weak bases like potassium acetate and sodium acetate could promoted the reaction with good yields (entries 11 and 12). Meanwhile, control experiments showed that both photocatalysts and light were essential to the success of the decarboxylative trifluoromethylation reaction (entries 13 and 14). Especially, it was worth noting this reaction shows excellent stereoselectivity (*E*/*Z* = 97/3).

With the optimal reaction conditions in hand, the substrate scope was investigated, and the corresponding results are listed in Table 2. Cinnamic acids bearing electron-donating substituents such as OMe, Me,OH could generate the products with high *E/Z* selectivities in good yields (**2a-2f**).

Table 1 Optimization of reaction conditions[a]



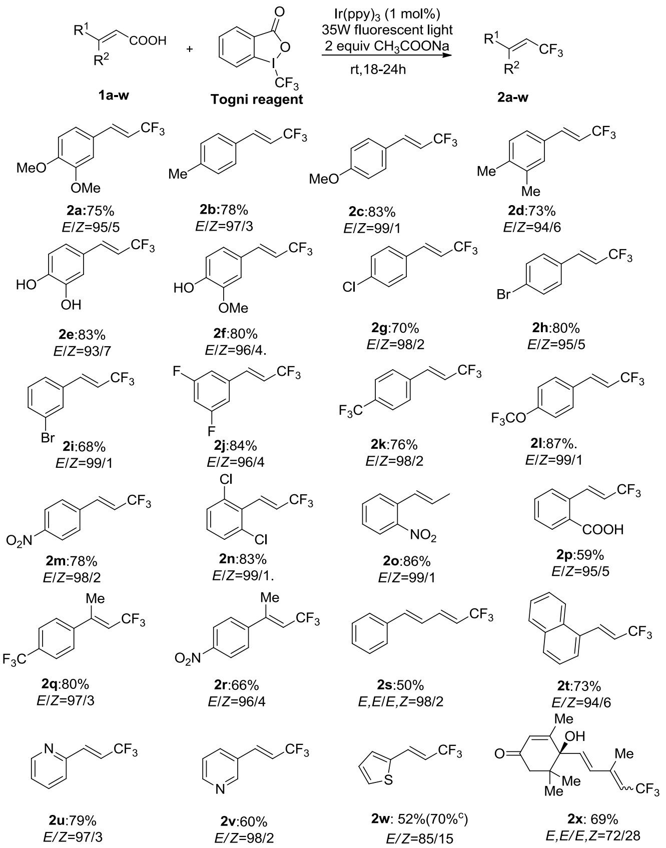
Entry	photocatalyst	additives	solvent	Yield(%)[b]
1	*fac*-Ir(ppy)$_3$	-	DMF	30
2	*fac*-Ir(ppy)$_3$	-	DCM	22
3	*fac*-Ir(ppy)$_3$	-	CH_3CN	13
4	*fac*-Ir(ppy)$_3$	-	DMSO	65
5	Ir(ppy)$_2$(bpy)PF$_6$	-	DMSO	19
6	Ir(ppy)$_2$(dtbbpy)BF$_4$	-	DMSO	26
7	Ru(bpy)$_3$Cl$_2$	-	DMSO	22
8	*fac*-Ir(ppy)$_3$	CH_3CH_2ONa	DMSO	62
9	*fac*-Ir(ppy)$_3$	NaOH	DMSO	trace
10	*fac*-Ir(ppy)$_3$	TsOH	DMSO	trace
11	*fac*-Ir(ppy)$_3$	CH_3COOK	DMSO	78
12	***fac*-Ir(ppy)$_3$**	**CH_3COONa**	**DMSO**	**83(75)[c]**
13	-	CH_3COONa	DMSO	N.P
14[d]	*fac*-Ir(ppy)$_3$	CH_3COONa	DMSO	N.P

[a] Reaction conditions: **1a** (0.2 mmol), Togni reagent (0.3 mmol), additives (0.4 mmol), photocatalyst (1 mol%), solvent (1 mL), 35 W fluorescent light bulb, 18 h, rt. [b] Determined by ^{19}F NMR analysis of the reaction mixture using perfluorobenzene as an internal standard. [c] Isolated yield. [d] In the dark.

In addition, various cinnamic acids bearing electron-withdrawing functional groups also showed good reactivities in this catalytic system (**2g-2l**). It was worth mentioning that Hu[4d] and Liu's[4e] copper-catalyzed decarboxylative trifluoromethylation catalytic system were ineffective for electron-deficient substrates. Much to our surprise, functional groups like NO_2 which was usually not tolerated in photoredox catalysis reaction system gave the desired product in good yields with high stereoselectivity in present system (**2m**). Subsequently, with substituent groups at the *ortho* position of the cinnamic acids, high yields (83-86%) were observed indicating the steric-bulk effect in the aromatic part could be ignored (**2n and 2o**). Moreover, the reaction had excellent chemoselectivity when different kinds of carboxylic acid groups (-COOH) were incorporated in one substrate (**2p**). Trisubstituted *α,β*-unsaturated carboxylic acids (**1q and 1r**) could afford the products in moder yields (66-80%). It was found that the substrates contain delocalized conjugated system also underwent the reaction smoothly (**2s and 2t**). In view of the prevalence of heteroarenes in drug molecules, we wondered whether our visible light photoredox system is compatible with heterocyclic substrates. Remarkably, the decarboxylative trifluoromethylation reaction with hetero-aromatic acid (**1u-w**) proceeded well to give the desired products in moderate yields (**2u-w**). To further demonstrate the generality of this visible light photoredox protocol, (+)-abscisic acid was tried, and it was found that the decarboxylative trifluoromethylation occurred well to afford the desired product **2x**. In general, the present photoredox system proved excellent from the viewpoint of functional group tolerance and substrate scope.

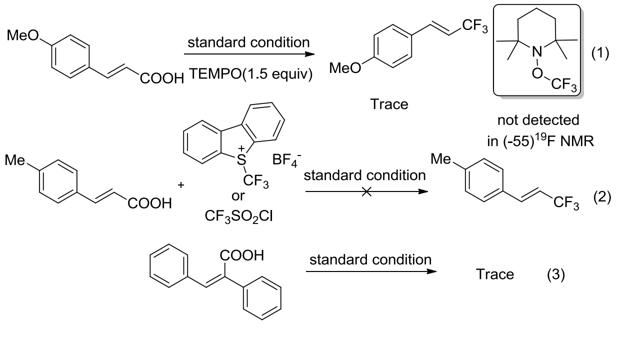
To understand the mechanism of this transformation, the radical inhibitor TEMPO was added in this reaction system [Scheme 2, Eq. (1)].[6c] Only trace desired product was detected, a result pointing toward a radical mechanism. It was strange that TEMPO−CF_3 adduct was not detected, indicating that other species rather than separate CF_3 radical might be at the start of these transformations.[9] In addition, other CF_3 reagents such as Umemoto reagent or CF_3SO_2Cl, which have been reported to generate a CF_3 radical in the presence of photoredox catalysts[10], did not work under the condition [Eq. (2)]. From this observation, we concluded that the use of hypervalent iodine types of Togni reagent was of key importance for the transformations. Besides, the observation that *α*-substituted acrylic acid did not work well in our system could help to exclude possible intermediates such as RC=CCOO-I(hypervalent)-CF_3(Ar) [Eq. (3)].

Table 2 Scope of substrates[ab]

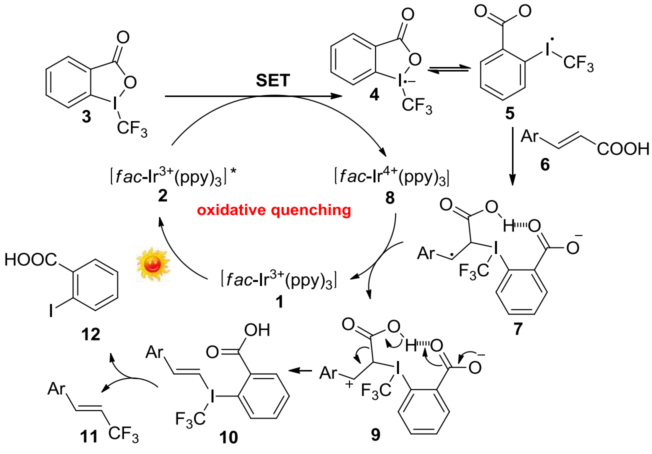


[a] The reactions were carried out with cinnamic acid (0.2 mmol), Togni reagent (1.5 equiv), sodium acetate (2 equiv), and *fac*-Ir(ppy)$_3$(1 mol%) in DMSO(1 mL) at room temperature, 36 W fluorescent light bulb, 18-24 h, unless otherwise mentioned. [b] yield of isolated product; *E/Z* ratio was determined by ^{19}F NMR spectroscopy of the crude product mixture.[c] yield in ^{19}F NMR.

Based on the above results, a plausible radical addtion/ decarboxylative reaction mechanism is shown in Scheme 2. Firstly, the ground state *fac*-Ir^{3+}(ppy)$_3$ **1** undergoes photoexcitation by visible light to form the excited state Ir^{3+*} **2**. Then Togni reagent 3 is reduced by resultant Ir^{3+*} **2** to give the corresponding radical anion **4**.[6c] Rapid collapse of **4** generate the unstable intermediate **5**, which soon undergoes radical addition to α,β-unsaturated carboxylic acids **6**, forming relatively radical intermediate **7**. **7** is further oxidized by Ir^{IV}(ppy)$_3$**8** ($E_{1/2red}$ = +0.77 V vs SCE in CH_3CN)[11] to give the key carbocation **9** through a single-electron oxidation. Intermediate **9** ultimately undergoes decarboxylation to give thermodynamically stable *E*-alkene intermediate **10**. Finally, reductive elimination form **10** would afford the desired species **11** and by-product **12**.[4d]



Scheme 2 Mechanistic experiments.



Scheme 3 Proposed mechanism.

Conclusions

In conclusion, a visible light-mediated system has been applied to the room temperature decarboxylative trifluoromethylation of *α,β*-unsaturated carboxylic acids. Importantly, preliminary mechanistic analyses suggest this novel reaction proceeds with a radical-type mechanism which may be different from the Cu-catalyzed protocol.[4d] Associated mechanisms are still being investigated in our laboratory.

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