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Photo-Induced Decarboxylative Amino-Fluoroalkylation of Maleic Anhydride

Youwen Sun, Guozhu Zhang*[a]

Dedication ((optional))

Abstract: A photo-induced decarboxylative three-component coupling reaction involving amine, maleic anhydride and fluorinated alkyl iodides has been developed, leading to synthetically valuable fluoroalkyl-containing acrylamides in a high *E* selectivity. A broad array of substrates including monoprotected amino acid are capable coupling partners. Preliminary mechanistic studies suggest a stepwise process. This reaction represents the first example of photo-induced decarboxylative difunctionalization of maleic anhydride.

Amides are ubiquitous in both simple and complex molecules such as drugs, polymers, enzymes, proteins, antibodies, and collagen – all molecules of high relevance to human lives.[1] There are many ways to prepare amides, but environmentally benign and green methodologies with significant reduction in waste and cost are still highly desired.[2] In this regard, transition-metal-catalyzed multicomponent reactions prove to be an ideal technology. Avoiding the synthesis of starting material, in a single operation, several new bonds are formed and new functionalities are introduced.[3] In the meantime, incorporation of fluorine atoms into organic motifs has a significant influence on the lipophilicity, metabolic stability, and bioavailability of organic molecules.[4] Fluoroalkylation using relatively mild fluoroalkyl halides as a fluorine source has been the focus of current research.[5] Therefore, more mild and practical catalytic systems need to be developed to provide a convenient strategy for the construction of fluorinated amides bearing functional groups for easy derivatization.

Recently, photoredox catalysis has emerged as a valuable alternative to the traditional initiator-promoted radical reactions, allowing the generation of active species under mild reaction conditions.[6] Photo-induced decarboxylative functionalization of readily available organocarboxylic acid is one of the well-established methodologies.[7] We were interested in developing one-step protocol for the difunctionalization of feed stock chemicals.[8] Herein, we disclose a novel, photoinduced three-component decarboxylative aminofluoroalkylation of maleic anhydride with fluorinated alkyl iodide and a series of amines, leading to synthetically useful fluorinated acrylamides. Notably, this transformation is highly stereoselective, as only *E*-product was isolated from the reaction. More importantly, bio-relevant amino acid derivatives are suitable substrate as well, rendering this methodology added synthetic value.

Maleic anhydride easily undergoes ring opening in the presence of amine.[9] The resulting *cis*-amide alkenylcarboxylic acid is potentially suitable substrate for decarboxylative functionalization. As far as we know, examples engaging two transformations of maleic anhydride in a single reaction have not been reported. We hypothesized that a suitable combination of base, amine, fluoroalkyl halide, photocatalyst and maleic anhydride could generate fluoroalkylated acrylamide through tandem ring opening and photo-induced decarboxylative fluoroalkylation.

Our investigations began with $Ru(bpy)_3Cl_2.6H_2O$ as the photocatalyst. The targeted product could be obtained in 14% yield using 3 equiv of ethyl difluoroiodoacetate, 2 equiv of maleic anhydride, 1 equiv of aniline and 2 equiv of sodium hydrogen carbonate as a base (Table 1, entry 1). Then, the adjustment of base to triethylamine (2 equiv) gave a moderate yield (Table 1, entries 1-5). Various solvents and photocatalysts were subsequently screened (Table 1, entries 5-12), the best results were obtained using tetrahydrofuran as solvent and triethylamine as the base. Further optimization of reaction conditions revealed that 8 equivalent of triethylamine was optimal (Table 1, entry 13-16). The results from reactions by varying the ratios of three reactants suggest excess of reactive maleic anhydride and ethyl difluoroiodoacetate benefit the product yield (Table 1, entry 17-20). Lastly, control experiments confirmed that light, photosensitizer and base are essential for the success of this chemistry, because when any one component is absent, no desired product was observed (Table 1, entries 21-23). The reaction scale could be increased to 1mmol under current set-up, a similar 78% yield was obtained (Table 1, entries 24).

With the optimized conditions in hand (Table 1, entry 15), we next examined the scope of amine (Scheme 1). Our protocol was found to readily accommodate a variety of anilines with different substitutions, including electron-neutral (Scheme 1, **1a**), electron-donating (Scheme 1, **1b**), and electron-withdrawing groups (Scheme 1, **1c-1f**). Halogens were well tolerated, offering opportunities for further decoration of the molecule (Scheme 1, **1d-1e**). In addition, heterocyclic substrates, such as 2-aminothiazole (Scheme 1, **1g**) was found to be competent substrate. Meanwhile, benzyl amine and simple aliphatic amine can also provide the target products (Scheme 1, **1h-1k**). Remarkably, bio relevant amino acids were converted into the desired products with moderate yields (Scheme 1, **1l-1r**), in those reactions the chiral centers remain intact. Notably,

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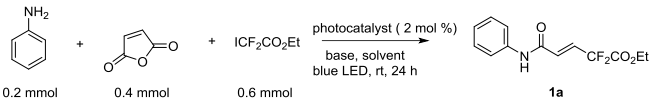
secondary amines are suitable substrates as well thus resulting in fully substituted amides (Scheme 1, **1t-1u**).

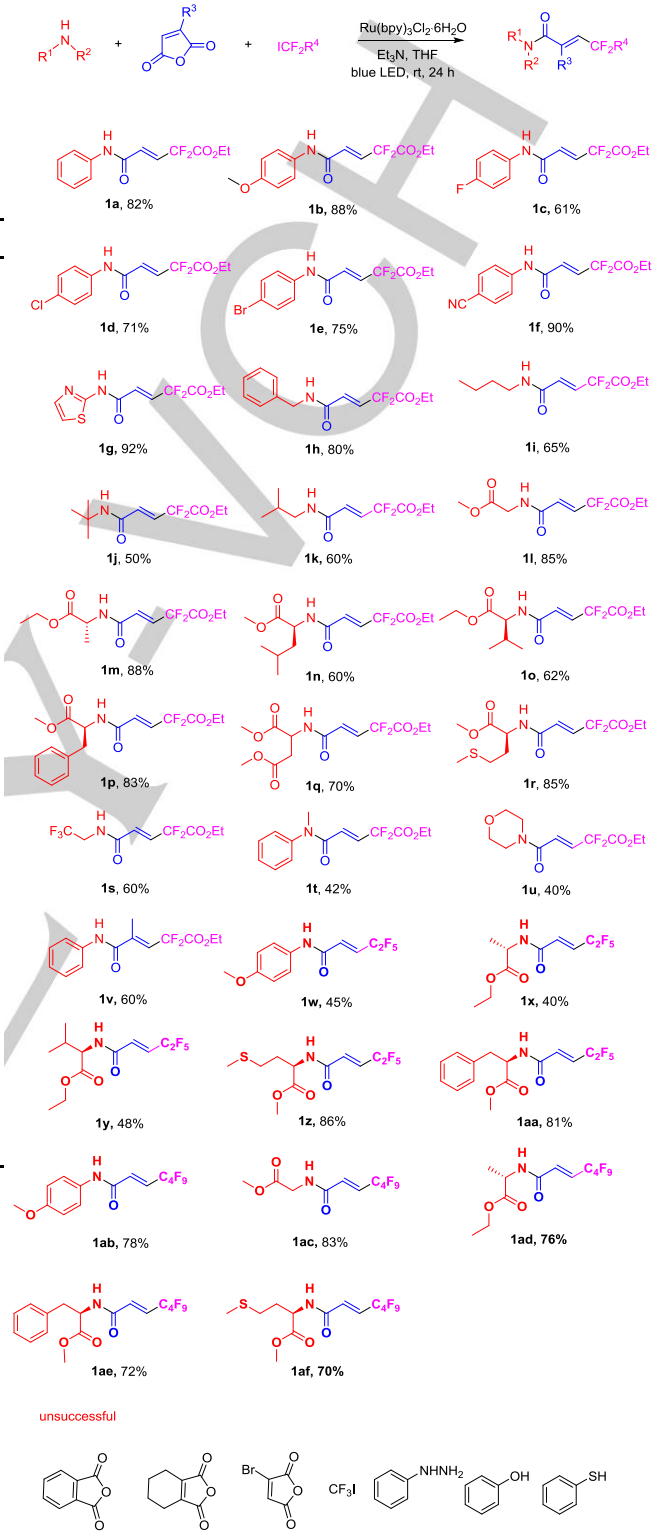
Table 1. Optimization of the reaction conditions.



Entry[a]	Photocatalyst	Base(equiv.)	Solvent	Yield/%[b]
1	$Ru(bpy)_3Cl_2.6H_2O$	$NaHCO_3$(2.0)	THF	14
2	$Ru(bpy)_3Cl_2.6H_2O$	Cs_2CO_3(2.0)	THF	36
3	$Ru(bpy)_3Cl_2.6H_2O$	DBU(2.0)	THF	24
4	$Ru(bpy)_3Cl_2.6H_2O$	$^iPr_2NEt$(2.0)	THF	30
5	$Ru(bpy)_3Cl_2.6H_2O$	Et_3N(2.0)	THF	57
6	$Ru(bpy)_3Cl_2.6H_2O$	Et_3N(2.0)	CH_3CN	40
7	$Ru(bpy)_3Cl_2.6H_2O$	Et_3N(2.0)	DCM	20
8	$Ru(bpy)_3Cl_2.6H_2O$	Et_3N(2.0)	DMF	30
9	$Ru(bpy)_3Cl_2.6H_2O$	Et_3N(2.0)	DMA	40
10	$Ru(bpy)_3Cl_2.6H_2O$	Et_3N(2.0)	Dioxane	20
11	$Ir(ppy)_3$	Et_3N(2.0)	THF	53
12	$Ir(dtbpy)_2(ppy)$	Et_3N(2.0)	THF	50
13	$Ru(bpy)_3Cl_2.6H_2O$	Et_3N(4.0)	THF	66
14	$Ru(bpy)_3Cl_2.6H_2O$	Et_3N(6.0)	THF	70
15	$Ru(bpy)_3Cl2.6H_2O$	Et_3N(8.0)	THF	82
16	$Ru(bpy)_3Cl_2.6H_2O$	Et_3N(10.0)	THF	71
17[c]	$Ru(bpy)_3Cl_2.6H_2O$	Et_3N(8.0)	THF	23
18[d]	$Ru(bpy)_3Cl_2.6H_2O$	Et_3N(8.0)	THF	41.
19[e]	$Ru(bpy)_3Cl_2.6H_2O$	Et_3N(8.0)	THF	22.
20[f]	$Ru(bpy)_3Cl_2.6H_2O$	Et_3N(8.0)	THF	15.
21	-	Et_3N(8.0)	THF	N.D.
22	$Ru(bpy)_3Cl_2.6H_2O$	-	THF	N.D.
23[g]	$Ru(bpy)_3Cl_2.6H_2O$	Et_3N(8.0)	THF	N.D.
24[h]	$Ru(bpy)_3Cl_2.6H_2O$	Et_3N(8.0)	THF	78

[a] Reactions were carried out in 0.2 mmol scale and the procedure was same as the general procedure. [b] Measured by ^1H NMR analysis using diethyl phthalate as internal standard. [c] The ratios of Aniline, maleoside, ethyl difluoroiodoacetate is 0.2mmol:0.2mmol:0.2mmol. [d] The ratios of Aniline, maleoside, ethyl difluoroiodoacetate is 0.2mmol:0.2mmol:0.4mmol. [e] The ratios of Aniline, maleoside, ethyl difluoroiodoacetate is 0.2mmol:0.4mmol:0.2mmol. [f] The ratios of Aniline, maleoside, ethyl difluoroiodoacetate is 0.4mmol:0.2mmol:0.2mmol. [g] No light. N.D. not determined. [h] Reactions were carried out in 1.0 mmol scale.

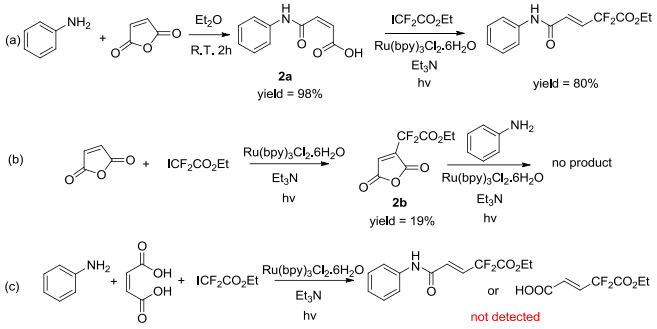
To further demonstrate the utility and generality of this novel reaction, we tried to replace the maleic acid glycosides, delightfully, citraconic anhydride also reacted well (scheme 1, **1v**).We then turned our attention to different fluoroalkyl iodides. Reactions of pentafluoroiodoethane and perfluoroiodobutane with aromatic amines (scheme 1, **1w**, **1ab**) and common amino acid esters (scheme 1, **1x-1aa**, **1ac-1af**) proceeded smoothly. For the example (**1t**, **1u**, **1w**, **1x**,**1y**) of low yield, it may be due to the instability of raw materials and reaction intermediates, which are easy to decompose. It is known methionine is not stable and easily oxidized, but the target product derived from methionine can be obtained successfully under standard conditions. However, our attempts to explore other hetero nucleophiles including hydroxy, thiol and phenylhydrazine were not successful under current reaction conditions.



Scheme 1. Scope studies with coupling partners.[a][b] [a] The reactions were carried out under these optimized conditions (Table 1, entry 15). [b] Isolated yield.

In order to elucidate the mechanism, a series of control experiments were performed as outlined in Scheme 2. The product could be obtained by a two-step procedure in equal

efficiency, suggesting a stepwise mechanism is viable (Scheme 2, eq a). The high *E* selectivity is possibly attributed to the following downstream decarboxylation. Without amine, a product through atom transfer radical addition-elimination (ATRE) reaction was obtained in good yield and no ring-opening or decarboxylative products were observed (eq b). Using maleic acid as substrate, no desired product was found (eq c).



Scheme 2. Control experiments for mechanistic study.[a][b] [a] The reactions were carried out under these optimized conditions (Table 1, entry 15). [b] The results were analyzed by GC/MS.

Then, the fluorescence quenching experiments were conducted–(See Supporting Information for details). we found that both halogenated alkane and triethylamine had the same quenching effect on photosensitizer, but the quenching coefficient of halogenated alkane (K_{SV} (ICF_2CO_2Et), 0.6 uM^{-1}) was much larger than that of triethylamine (K_{SV} (Et_3N), 0.05 uM^{-1}), so halogenated hydrocarbon might be the major quenching agent. A reaction quantum yield was measured to be φ= 3.2%, indicating the radical chain mechanism is less likely. Based on above results, a plausible mechanism is outlined in Figure 1. Photoexcitation of $Ru(bpy)_3Cl_2.6H_2O$ upon blue irradiation results in a metal-to-ligand charge transfer (MLCT) excited state.[11] Then difluoroalkyl radical is generated through oxidative quenching. Next, Aniline attacks maleate to produce *cis*-oleic acid, which captures fluoroalkyl radical to afford intermediate B. Finally, the product is obtained by oxidative decarboxylation. It is worth mentioning that the last step is highly stereospecific as only *E*-products were observed[12], We think that it's mainly thermodynamic that leads to a more stable E structure.

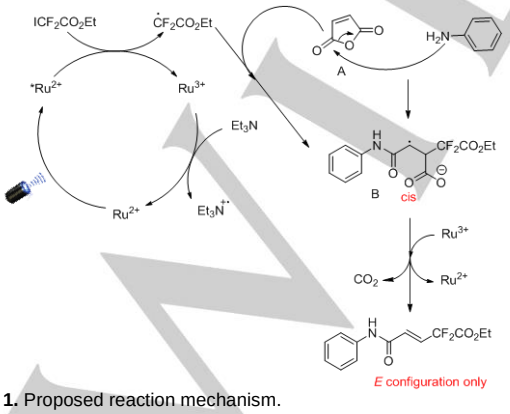
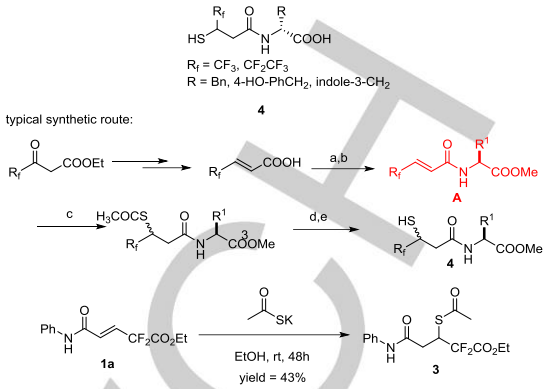


Figure 1. Proposed reaction mechanism.

The highly functionalized products could serve as useful platform for further derivatizations. The synthetic potential was briefly shown in Scheme 3. Amino acid bonded compound **3**, an analogue of advanced intermediate leading to dual ACE/NEP inhibitors **4**, could be constructed in one step through our method. In contrast, literature procedure required a four step synthesis from not easily available starting material.[13]



Scheme 3. Representative dual ACE/NEP inhibitors analogues 4 and typical synthetic route. Reagents and conditions: (a) phthaloyl dichloride, 180 ºC, (70-77%); (b) H-AA-OMe, TEA, DCM, 0 ºC (73-96%); (c) AcSH, EtOH, rt (rd = 1:1, 30-89%); (d) for R^1 = 4-*tert*-BuO-Ph-CH2-, 20% TFA, DCM, rt, 1 h (98%); (e) degassed 2 N NaOH in MeOH, 0 ºC, 1 h (quantitative).

In summary, we have reported a highly effective and synthetically convenient method of decarboxylative three-component aminofluoroalkylation reaction of maleic anhydride induced by visible light**.** The reaction couples are readily available Maleic anhydride, a variety of fluorinated alkyl halides, and a broad range of amines. The resulting fluoroalkylated acrylamide are valuable building block which could find applications in synthetic and medicinal chemistry.

Experimental Section

General procedure of the reaction: In a dried sealed tube, under N_2 atmosphere, $Ru(bpy)_3Cl_2.6H_2O$ (3.0 mg, 0.004 mmol, 2 mol %) and maleic acid glycosides (0.4 mmol, 2.0 equiv.) were dissolved in THF (2.0 mL), then anilin (0.2 mmol, 1.0 equiv.), ethyl difluoroiodoacetate (0.6 mmol, 3.0 equiv.) and triethylamine (1.6 mmol, 8.0 equiv.) were added in sequence.The mixture was placed 5 cm away from the 35-watt blue lamp and stirred at 25 ºC for 24 hours. After that, the mixture was filtered short silica gel column and concentrated under vacuum. The residue was purified by column chromatography on silica gel with a gradient eluent of petroleum ether (PE) and ethyl acetate (EA) to afford the product.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: photo-induced • three-component • decarboxylative • fluoroalkyl-containing acrylamides • high *E* selectivity

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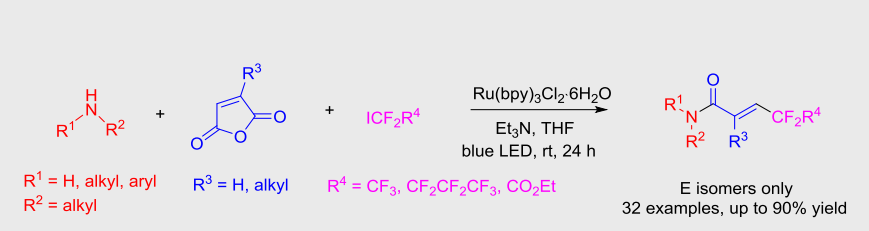

Youwen Sun, Guozhu Zhang[a]*

Page No. – Page No.

Photo-Induced Decarboxylative Amino-Fluoroalkylation of Maleic Anhydride

A photo-induced decarboxylative three-component coupling reaction involving amine, maleic anhydride and fluorinated alkyl iodides has been developed, leading to synthetically valuable fluoroalkyl-containing acrylamides in a high E selectivity. A broad array of substrates including monoprotected amino acid are capable coupling partners. Preliminary mechanistic studies suggest a stepwise process. This reaction represents the first example of photo-induced decarboxylative difunctionalization of maleic anhydride.