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Communication

Visible light photocatalytic decarboxylative monofluoroalkenylation of α-amino acids with *gem*-difluoroalkenes†

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α-Amino acids are among the most common biologically active molecules in nature, and their functionalization has attracted much attention. In this communication, a novel, efficient and general visible-light photocatalytic decarboxylative monofluoroalkenylation of *N*-protected α-amino acids with *gem*-difluoroalkenes is reported, affording the corresponding α-amino monofluoroalkenes which might find applications in medical chemistry and materials sciences. The reaction proceeded at room temperature with high efficiency and tolerance of various functional groups.

Fluorinated organic compounds play an important role in pharmaceutical, medicinal[1] and agrochemical sciences[2] owing to the small size and high electronegativity of fluorine and the unique chemical and physical properties of fluorine-containing structural motifs. About 20-25% of pharmaceuticals and 30-40% of agrochemicals on the market are estimated to be molecules containing fluorine.[3] In addition, these compounds occupy an important place in materials science.[4] Therefore, construction of fluorine-containing compounds has been a highly topical area of research. As a typical representative of fluorinated compounds, monofluoroalkenes are regarded as nonhydrolyzable amide bioisosteres[5] and their lipophilic properties prompt chemists to develop synthetic approaches to monofluoroalkenes. Among the starting materials for the synthesis of monofluoroalkenes, *gem*-difluoroalkenes are readily available and versatile substrates,[6] and their C-F bond functionalization with boronic acids,[7] heteroarenes,[8] alkyl Grignard reagents[9] have been explored under transition metal catalysis. α-Amino acids widely occur in nature, are available in large scale, and their chemical transformations deliver diverse compounds of interest. Recently, visible light photoredox catalysis as a clean, efficient and accessible strategy has exhibited great potential in development of novel reactions,[10] and our research group has also developed some valuable visible-light photocatalytic chemical transformations.[11] Particularly, visible light photoredox decarboxylative couplings of *N*-protected α-amino acids were reported by MacMillan's group[12] and us.[11g-l] Very recently, Hashmi and co-workers described a visible light photoredox C(sp^3)-H monofluoroalkenylation of dimethylanilines and trialkyl amines via an oxidation/deprotonation sequence.[13] We realized that fluorinated molecules containing amino acid fragments would be of great interest for further derivatization to diverse compounds, so we here report our work toward visible light photoredox decarboxylative monofluoroalkenylation of *N*-protected α-amino acids with *gem*-difluoroalkenes.

Reaction of *N*-*tert*-butoxycarbonyl proline (*N*-Boc-Pro) (**1a**) with 1-(2,2-difluoro-1-phenylethenyl)benzene (**2a**) was used as the model to optimize conditions including photocatalysts, bases, solvents and time (see Table S1 in Supporting Information for the details). The results showed that the optimal photoredox conditions are as follows: 2.0 mol% Ir[dF(CF_3)ppy]$_2$(dtbbpy) (**A**) as the photocatalyst, Li_2CO_3 as the base, and DMSO as the solvent at room temperature under argon atmosphere. After establishing the optimal photocatalytic system, we first investigated the scope of *N*-protected α-amino acids. As shown in Table 1, both *N*-Boc-Pro and *N*-Cbz-Pro (Cbz = benzyloxycarbonyl) gave the corresponding products in satisfactory yields (see **3a** and **3b**), and the former was a better substrate. Other *N*-Boc-protected amino acids, *N*-Boc-pipecolic acid, *N*-Boc-glycine, *N*-Boc-alanine, *N*-Boc-phenylalanine, *N*-Boc-serine containing hydroxyl and *N*-Boc-methionine containing thioether, were attempted, and they also were good substrates (see **3c-h**). Specifically, the fact that naturally occurring monoprotected amino acids could be used is of high interest for further functionalization and shows the advantage of our method compared to previous reports. Subsequently, various substituted *gem*-difluoroalkenes were screened. *Gem*-difluoroalkenes derived from ketones (see **3i-p**) provided similar results to 1-(2,2-difluoro-1-phenylethenyl)benzene (**2a**), and unsymmetrical *gem*-difluoroalkenes provided tetrasubstituted monofluoroalkenes as mixtures of *E* and *Z* isomers. However, reaction of *N*-benzyl-proline with 4,4'-(2,2-difluoroethene-1,1-diyl)bis(chlorobenzene) afforded the expected product in lower yield (see **3k**). Next, *gem*-difluoroalkenes derived from aldehydes were explored, and they afforded the corresponding trisubstituted monofluoroalkenes in good to excellent yields as mixtures of *E* and *Z* isomers (see **3q-ab**) without formation of alkynyes as side-products via a dehydrofluorination. Fortunately, *E* and *Z* isomers of most products could be separated by simple silica gel column chromatography (see Supporting Information for the details). We found that the electronic effects of the substituents on the

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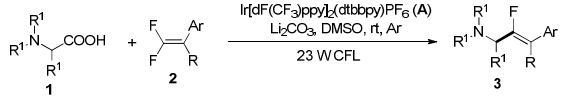
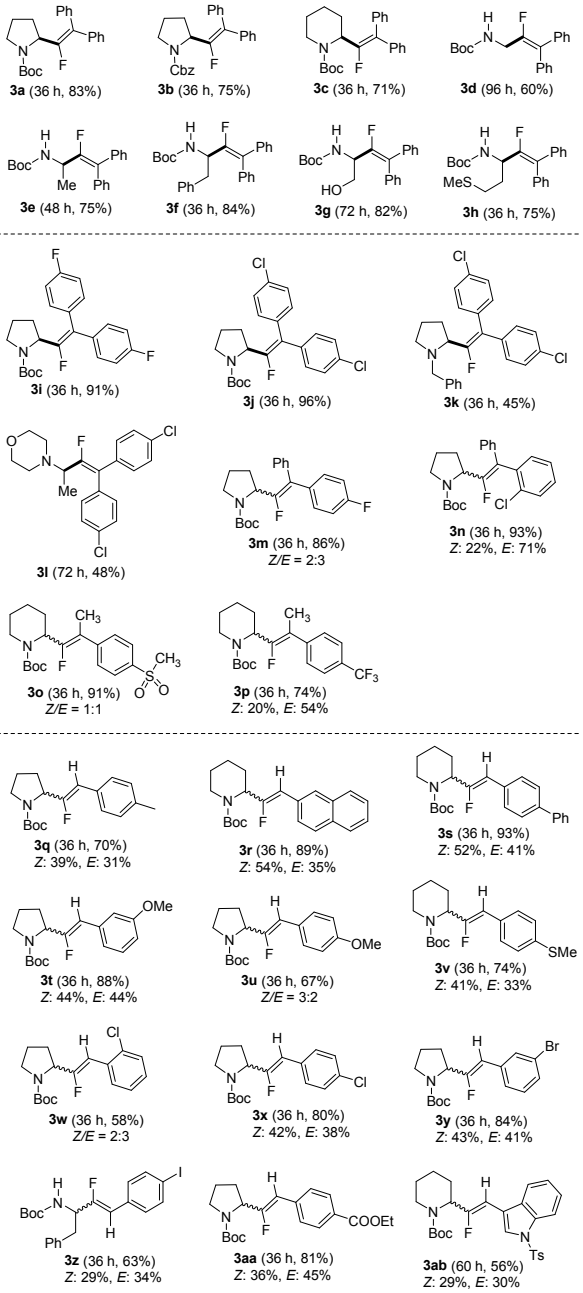
aromatic units in **2** had no obvious influence on the reaction efficiency. This visible-light photocatalytic decarboxylative monofluoroalkenylation of *N*-protected α-amino acids showed tolerance of numerous functional groups including C-F, C-Cl, C-Br and C-I bonds, amides, hydroxyl, ethers, thioethers, sulfonyl and sulfonamide groups. Unfortunately, *gem*-difluoroalkenes derived from dialkyl ketones and aliphatic aldehydes did not work under the present conditions.

Table 1 Substrate scope on visible-light photocatalytic decarboxylative monofluoroalkenylation of *N*-protected α-amino acids (**1**)[a]



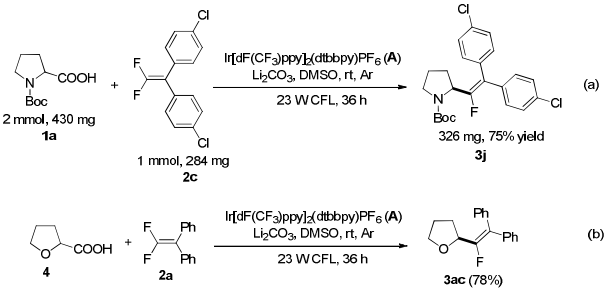
1 **2** **3**

3 (Time, Yield[b])



[a] Reaction conditions: irradiation of visible light with 23 W CFL and argon atmosphere, *N*-protected α-amino acid (**1**) (0.4 mmol), *gem*-difluoroalkene (**2**) (0.2 mmol), PC (**A**) (4 μmol), Li_2CO_3 (0.6 mmol), DMSO (2.0 mL), temperature (rt, ~25 °C), time (36-72 h) in a sealed Schlenk tube. [b] Isolated yield. Z/E ratios were determined by ^{1}H NMR spectroscopy or yields of the isolated isomers. Cbz = benzyloxycarbonyl.

The reaction could be scaled up from 0.20 mmol to 1.0 mmol using *N*-Boc-Pro (**1a**) as partner, and the reaction proceeded well affording **3j** in good yield (326 mg, 75% yield) (Scheme 1a). We also showed that coupling of 2-tetrahydrofuroic acid (**4**) with 1-(2, 2-difluoro-1-phenylethenyl)benzene (**2a**) was feasible under the standard conditions and the corresponding product **3ac** was obtained in 78% yield (Scheme 1b).



Scheme 1 (*a*) Scale-up experiment for coupling of *N*-Boc-Pro (**1a**) with 4,4'-(2,2-difluoroethene-1,1-diyl)bis(chlorobenzene) (**2c**); (*b*) Coupling of 2-tetrahydrofuroic acid (**4**) with 1-(2,2-difluoro-1-phenylethenyl)benzene (**2a**) under the standard conditions.

To explore the mechanism on the visible-light photocatalyic decarboxylative monofluoroalkenylation of *N*-protected α-amino acids, the reaction of *N*-Boc-proline (**1a**) with 1-(2,2-difluoro-1-phenylethenyl)-4-fluorobenzene (**2a**) was carried out in the presence of two equivalents of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) as the radical-trapping agent under the standard conditions, and no reaction was observed, suggesting that the reaction proceeded via a radical pathway. Given that the excited state of Ir[dF(CF_3)ppy]$_2$(dtbbpy) (**A**) is a strong oxidant {$E_{1/2}^{red}$[*Ir^{III}/Ir^{II}] = + 1.21 V vs SCE},[12d] the substrate *N*-Boc-Pro (**1a**) could be oxidized efficiently ($E_{1/2}^{red}$ = + 0.95 V vs SCE).[12d] Then, the reduction of 1-(2,2-difluoro-1-phenylethenyl)-4-fluorobenzene (**2a**) ($E_{1/2}^{red}$ = - 1.04V vs SCE)[13] should proceed favourably via single electron transfer from the Ir^{II} complex {$E_{1/2}^{red}$[Ir^{III}/Ir^{II}] = - 1.37 V vs SCE}.[13] According to the experimental results above and previous reports,[13] a possible mechanism on the visible light-mediated decarboxylative monofluoroalkenylation is proposed in Scheme 2. Under irradiation of visible light, photocatalyst Ir^{III} is excited to *Ir^{III} which is a strong oxdant. The *N*-Boc proline (**1a**) is deprotonated by the base (Li_2CO_3) and further oxidized by *Ir^{III} delivering the transient α-aminoalkyl radical **I** and Ir^{II} via single electron transfer (SET), along with the departure of carbon dioxide. Subsequently, reduction of *gem*-difluoroalkenes by Ir^{II} via SET provides a persistent radical anion that decomposes to the monofluoroalkenyl radical **II** and a fluorine anion, possibly under assistance of the lithium cation, regenerating photocatalyst Ir^{III}. Finally, radical-radical cross-coupling between **I** and **II**[13] affords the target product (**3a**).

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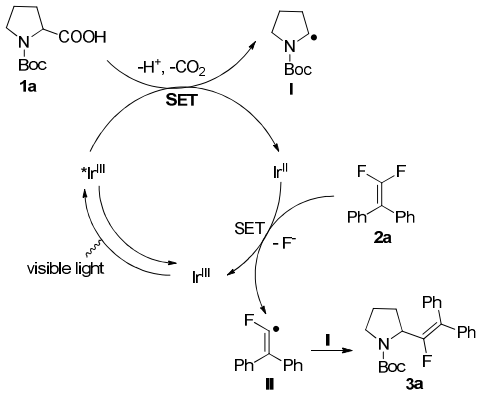
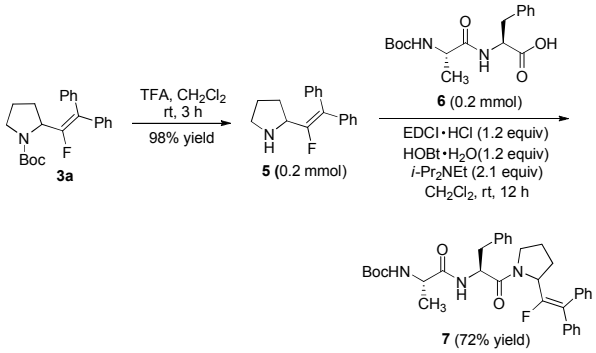


Scheme 2 A proposed mechanism for the decarboxylative monofluoroalkenylation of *N*-protected α-amino acids.

Interestingly, the obtained monofluoroalkenylation products above contain amino acid fragments which could be further derivatized after the protective group removal. For example, deprotection of product **3a** with trifluoroacetic acid (TFA) in CH_2Cl_2 affords **5**, and coupling of **5** with dipeptide *N*-Ala-Phe (**6**) gave **7** (Scheme 3). Therefore, our monofluoroalkenylation method should provide opportunity for synthesis of diverse fluorinated compounds and peptidomimetics.



Scheme 3 Application of the synthesized product (**3a**).

In summary, we have developed a mild and practical visible-light photocatalytic decarboxylative monofluoroalkenylation of *N*-protected *α*-amino acids with *gem*-difluoroalkenes. The reaction smoothly proceeded under visible-light photocatalysis. Both α-amino acids and *gem*-difluoroalkenes are readily available or can be prepared on scale with high efficiency. In addition, the resulting products, α-amino monofluoroalkenes, are useful building blocks in pharmaceutics, agrochemical and materials sciences.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Synthetic procedures, characterization data and ^{1}H, ^{13}C, ^{19}F NMR spectra of these synthesized compounds. See DOI: 10.1039/b000000x/

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Graphical abstract

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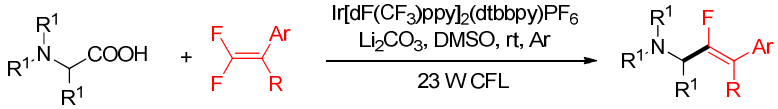

A novel, efficient and general visible-light photocatalytic decarboxylative monofluoroalkenylation of *N*-protected α-amino acids with gem-difluoroalkenes is reported, affording the corresponding α-amino monofluoroalkenes. The reaction proceeded at room temperature with high efficiency and tolerance of various functional groups.