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Photoredox Decarboxylative 3-Fluoroallylation of α-Amino Acids

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The photocatalytic decarboxylation of α-amino acids is an effective route to α-aminoalkyl radicals, which is also amenable to the derivatization of peptides through selective C—C bond formation at the C-terminus. It is reported that, in the presence of an iridium photocatalyst, allylic difluorides are suitable radical traps to capture α-aminoalkyl radicals produced from α-amino acids, ultimately amounting to a defluorinative 3-fluoroallylation reaction. The catalytic system is applied to the derivatization of a wide breadth of *N*-protected amino acids and dipeptides in high yields, and the transformation displays great functional group tolerance. α-Amino acids of all substitution levels at the α-carbon led to the desired products in high yields. Post-functionalization of the monofluoroalkene-containing products reveals the potential to attain fluorine-containing organic compounds of greater complexity.

1. Introduction

The quest for greener synthetic methodologies to construct organic compounds pointed to carboxylic acids and their derivatives as precursors of choice for carbon-centered radicals,[1,2] which is further reinforced by the easy access to carboxylic acids.[3] These carbon-centered radicals are generated upon decarboxylation,[1–4] which can be accomplished via the 1-electron reduction of redox-active esters and the fragmentation of the resulting intermediate,[1,5] or directly from carboxylate ions via 1-electron oxidation to acyloxy radicals.[1,6] The latter paves the way to using α-amino acids as direct precursors of α-aminoalkyl radicals, which can be achieved through photocatalysis in efforts to forge new C—C bonds.[7,8] Decarboxylative coupling reactions are also a powerful mode of late-stage modification of peptides, which can be applied to the synthesis of peptide-based pharmaceuticals.[9]

We wished to merge the decarboxylative reactivity of α-amino acids with our interest toward the installation of fluorinated units onto organic compounds, particularly monofluoroalkenes. The frequent incorporation of fluorine into pharmaceuticals[10] and agrochemicals[11] is a direct consequence of the strength of the C—F bond[12] and changes to physicochemical properties induced by the high electronegativity of fluorine.[13] As for monofluoroalkenes, they can strategically be used as non-hydrolyzable isosteres of peptide bonds and mimics of enols.[14,15] One convenient synthetic route to monofluoroalkenes is the partial defluorination of polyfluorinated precursors.[16–18] However, the challenge resides in achieving partial defluorination rather than exhaustive defluorination as residual C—F bonds are typically weakened after each defluorinative event.[12,18] A report documented the photocatalytic coupling of α-amino acids and *gem*-difluoroalkenes, resulting in decarboxylative/defluorinative 1-fluorovinylation reactions (**Scheme 1**a).[19] Inspired by our previous success of trapping α-aminoalkyl radicals generated from *N*-alkylanilines with allylic difluorides,[20] we hypothesized that α-amino acids could be engaged in analogous redox-neutral photocatalytic transformations. This would present the advantage of greatly expanding the pool of radical precursors by precluding the need for full substitution at nitrogen and for at least one aryl substituent. In this case, exhaustive defluorination is curbed by the change of hybridization from C(sp^3)—F to C(sp^2)—F in the product.[20,21] As such, we report herein the decarboxylative/defluorinative 3-fluoroallylation reaction of α-amino acids (Scheme 1b).

2. Results and Discussion

Optimization studies were conducted with cyclic allylic difluoride **1** and *N*-(*tert*-butoxycarbonyl)-L-phenylalanine (Boc-L-Phe-OH) as model substrates, resulting in the formation of fluorinated homoallylamine **2a** (**Table 1**). We aimed to optimize with this amino acid because the reactive intermediate is a 2° radical, which generally led to lower conversions in similar radical allylic substitution reactions of allylic difluorides.[20] However, unlike in our previous work using anilines as radical precursors,[20] photocatalyst $Ru(bpy)_3Cl_2{\cdot}6H_2O$ led to no product formation (**entry 1**). Likewise, $Ir(ppy)_3$ showed no conversion when Li_2CO_3 and DMSO were used as the base and solvent, respectively (**entry 2**). While [Ir(dtbbpy)$(ppy)_2$] produced a low yield, Ir[dF(CF_3)ppy]$_2$(dtbbpy)

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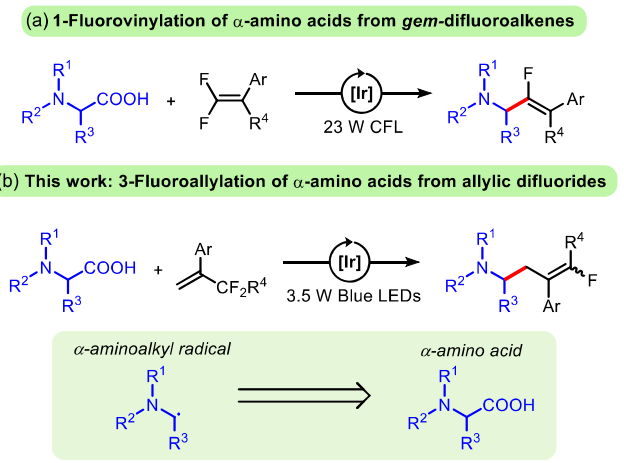
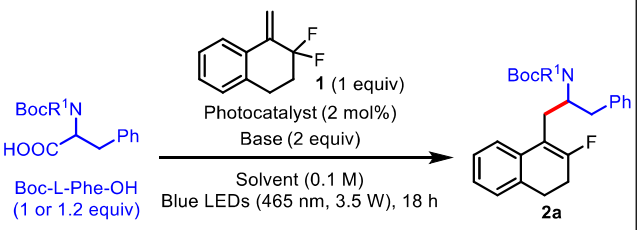


Scheme 1. Photocatalytic decarboxylative/defluorinative 1-fluorovinylation and 3-fluoroallylation of α-amino acids.

Table 1. Key optimization data for the photocatalytic reaction between Boc-L-Phe-OH and allylic difluoride 1.



Entry	Photocatalyst	Base	Amino acid [equiv]	Solvent	Yield[a] [%]
1	$Ru(bpy)_3Cl_2•6H_2O$	Li_2CO_3	1	DMSO	0
2	$Ir(ppy)_3$	Li_2CO_3	1	DMSO	0
3	$[Ir(dtbbpy)(ppy)_2]$	Li_2CO_3	1	DMSO	25
4	$[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$	Li_2CO_3	1	DMSO	71
5	$[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$	Li_2CO_3	1.2	DMSO	82
6	$[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$	Li_2CO_3	1.2	DMF	50
7	$[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$	Na_2CO_3	1.2	DMSO	91
8	**$[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$**	**Na_2CO_3**	**1.2**	**DMF**	**93**

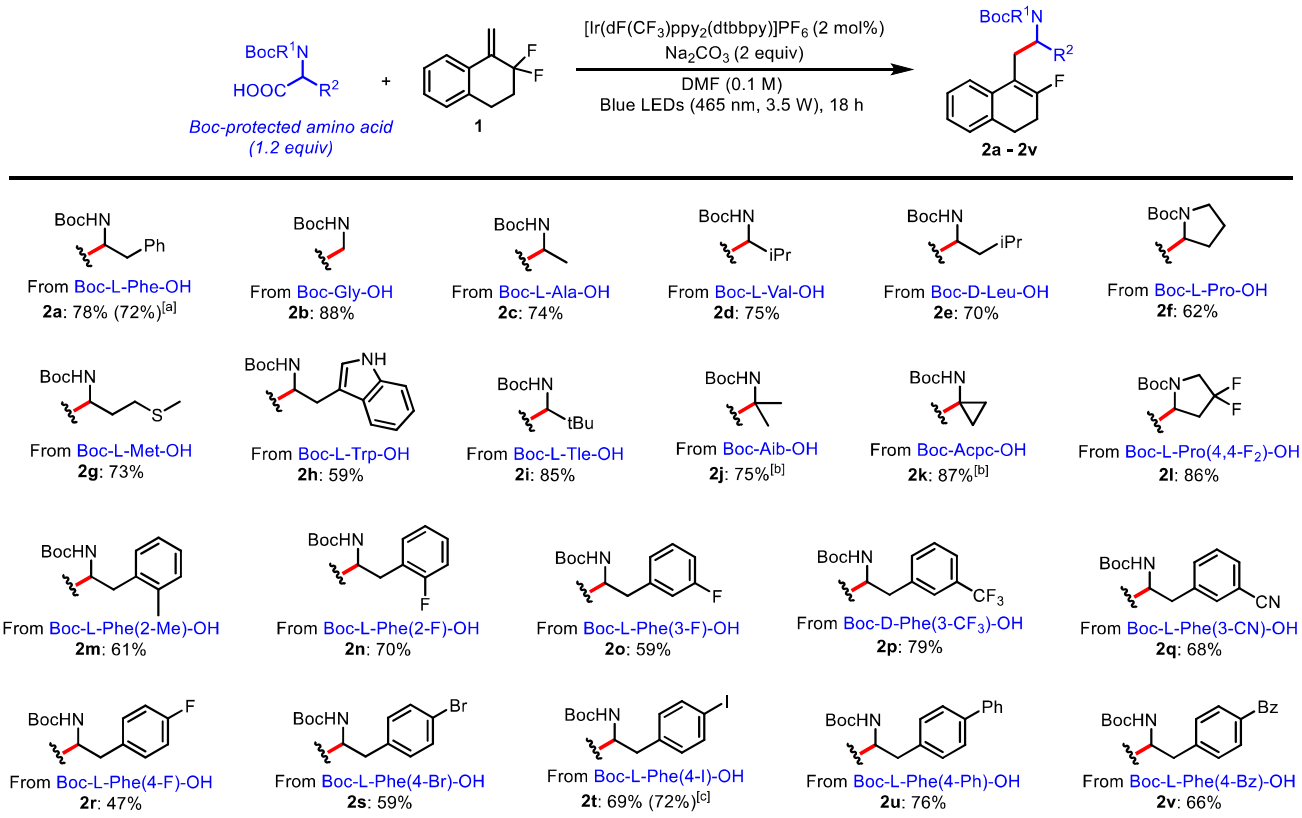
[a]Estimated by ^{19}F NMR spectroscopy using 2-fluoro-4-nitrotoluene as internal standard.

PF_6 was found to be the most efficient photocatalyst (**entries 3–4**). Increasing the stoichiometry of the amino acid from 1 to 1.2 equivalents increased the yield by a meaningful amount and was deemed preferable (**entry 5**). Further base and solvent screening was conducted and revealed that Na_2CO_3 was a superior base to Li_2CO_3, especially when DMF was used as solvent, amounting to a 93% NMR yield of **2a** (**entries 6–8**). A more detailed optimization can be found in the electronic supplementary information.

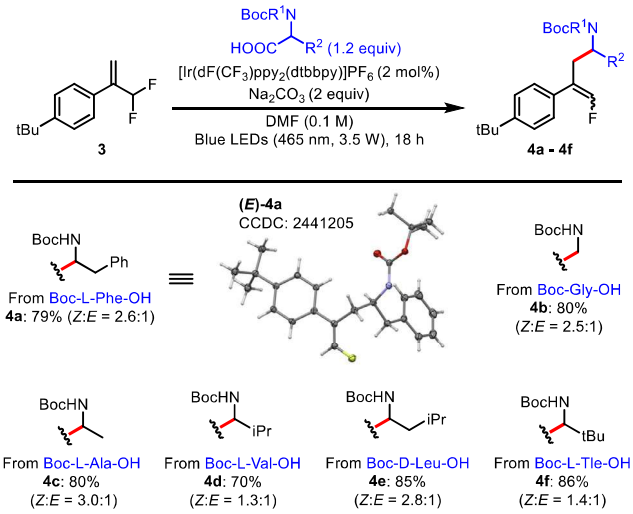
With the optimized reaction conditions in hand, we decided to scope out the range of Boc-protected amino acids that can react with cyclic allylic difluoride **1** (**Scheme 2**). Under standard conditions, **2a** was isolated with a 78% yield using Boc-L-Phe-OH. By switching the limiting reagent from the allylic difluoride to the amino acid, the same product was isolated with a 72% yield. This manipulation of stoichiometry highlights the adaptability of the method toward choosing which reagent to use in excess based on the difficulty to synthesize the precursors. As it could be expected as it produces a 1° radical intermediate, using Boc-Gly-OH produced **2b** with the best overall yield (88%). Other canonical amino acids with carbon side chains produced good yields (**2c-2e,** 70–75%), and even using the cyclic amino acid derivative Boc-L-Pro-OH gave **2f** with a moderate yield (62%). The heteroalkyl and heteoaryl side chains of Boc-L-Met-OH and Boc-L-Trp-OH did not conflict with the reactivity, forming **2g** and **2h** in 73% and 59% yields, respectively.

Non-canonical amino acid derivatives were then explored to develop a better understanding of functional group tolerance. The *tert*-butyl side chain of Boc-L-Tle-OH did not hinder reactivity as **2i** formed in high yield (85%). Despite going through a 3° radical intermediate, **2j** and **2k** were also produced with high yields provided that the reaction time was extended to 72 h. Boc-L-Pro(4,4-F_2)-OH was used in the reaction to produce **2l** with an 86% yield. Similar 3,3-difluoropyrrolidine motifs have been incorporated in pharmaceuticals such as Gosogliptin[22] and in ^{19}F-NMR-based probes for protein conformational analysis.[23] Next, we aimed to test out different *N*-Boc-protected phenylalanine derivatives as a method to highlight functional group tolerance and examine the effect that electron-rich and electron-poor substituents have on reaction success. Product **2m** was synthesized with an *ortho*-methyl derivative of phenylalanine with a 61% yield despite the increased steric hindrance. Having a fluorine atom on the *ortho* or *meta* positions of the phenyl ring respectively produced **2n** and **2o**, both in comparably good yields. Strong electron-withdrawing groups such as trifluoromethyl and cyano groups at the *meta* position were well tolerated, and **2p** and **2q** were synthesized in 79% and 68% yields, respectively. Products **2r**, **2s**, and **2t**, which all feature a halogen substituent (fluorine, bromine, iodine) at the *para*-position, were all successfully prepared. In the case of the iodo derivative **2t**, the reaction was repeated on a 1.00 mmol scale, which produced a slightly better yield when compared to the reaction performed on a smaller scale (72% vs 69%, respectively). Finally, phenylalanine derivatives that incorporated phenyl and benzyl groups at the *para* position gave **2u** and **2v** with 76% and 66% yields, respectively.

Next, we aimed to probe the reaction using acyclic allylic difluoride **3**, which displayed good reactivity without any further reaction optimization required. However, performing the reaction with an acyclic substrate resulted in product formation as a mixture of *Z* and *E* alkene isomers, which can be fully separated by column chromatography (**Scheme 3**). Using Boc-L-Phe-OH as the radical precursor, **4a** was synthesized with a 79% yield, and a *Z*:*E* ratio of 2.6:1. The configuration of the alkene was confirmed by X-ray crystallography via analysis of a sample of (***E***)-**4a**.[24] Compounds **4b** and **4c** were synthesized with Boc-Gly-OH and Boc-L-Ala-OH, respectively, both giving an 80% yield with *Z*:*E* ratios greater than 2.5:1. Expanding the size of the alkyl chain



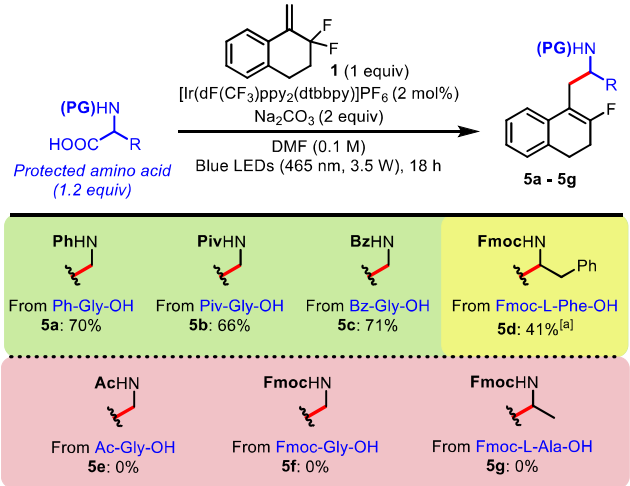
Scheme 2. 3-Fluoroallylation of α-amino acids with cyclic allylic difluoride **1**. a) Inverted stoichiometry (1.2 equiv of **1**, 1.0 equiv of amino acid). b) Reaction ran for 72 h. c) Reaction performed on a 1.00 mmol scale.



Scheme 3. 3-Fluoroallylation of α-amino acids with acyclic allylic difluoride **3**.

to isopropyl and isobutyl groups gave **4d** (70%) and **4e** (85%). Noteworthy, stereoselectivity for the formation of **4d** was greatly diminished, likely due to α-branching within the substituent. Finally, **4f** was synthesized when Boc-L-Tle-OH was used, giving the best overall yield for these substrates (86%), with a *Z*:*E* ratio of 1.4:1 that reinforces the presumed effect of α-branching on stereoselectivity.

Most reports of photoredox-catalyzed decarboxylation of α-amino acids utilize the Boc protecting group on the nitrogen atom. We sought to provide additional insights regarding the use of other substituents or protecting groups on nitrogen in decarboxylative functionalization reactions of α-amino acids such as our method (**Scheme 4**). When combined to **1**, *N*-phenylglycine led to a 70% yield of **5a**. As such, a free N—H bond was tolerated, unlike in the reactions done with *N*-alkylanilines.[20] We next looked into the use of a pivaloyl-protected α-amino acid (Piv-Gly-OH), which successfully produced **5b** with a 66% yield. Likewise, a benzoyl derivative (Bz-Gly-OH) led to the formation



Scheme 4. Reactivity trends with various protecting groups on nitrogen. a) Reaction ran for 72 h.

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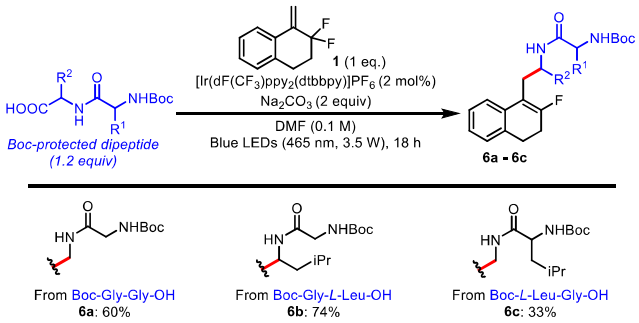
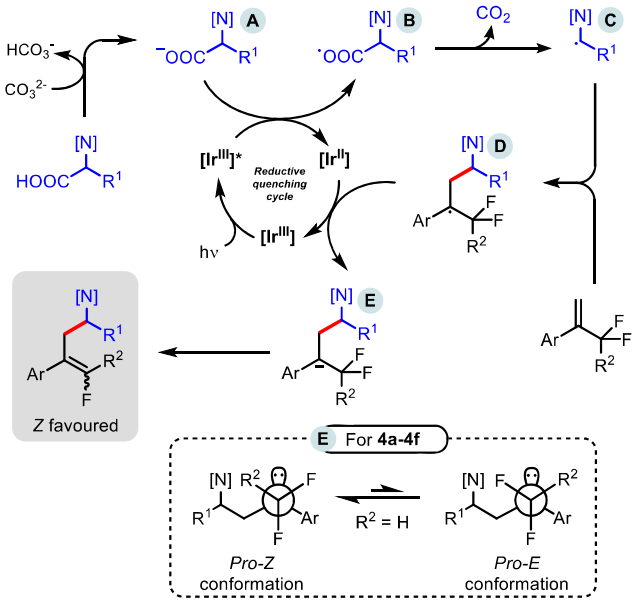
of **5c** with a 71% yield. To the contrary, an acetyl protecting group was not tolerated as **5e** was not formed upon using Ac-Gly-OH as the α-aminoalkyl radical precursor. The use of an Fmoc group gave contrasting results as while Fmoc-L-Phe-OH led to the formation of **5d** (41%) upon extending the reaction time to 72 h, neither **5f** nor **5g** were formed upon using Fmoc-Gly-OH or Fmoc-Ala-OH. We hypothesize that the poor results obtained with acetyl and Fmoc-protecting groups could be due to HAT competing with addition of the α-aminoalkyl radical to the allylic difluoride. Indeed, the acetyl group has hydrogens α to the carbonyl, unlike the pivaloyl and benzoyl groups. For the Fmoc group, a hydrogen atom is at a bis-benzylic site and could likely be engaged in HAT. As no additional fluorinated side products were identified, the radicals obtained after HAT (an α-carbonyl radical and a fluorenyl radical, respectively) may be insufficiently nucleophilic[25] to add to the allylic difluoride.

Next, we aimed to expand the reaction to include Boc-protected dipeptides as potential starting materials in the photocatalyzed 3-fluoroallylation reaction (**Scheme 5**). When the reaction was performed with Boc-protected glycylglycine (Boc-Gly-Gly-OH), **6a** was successfully synthesized with a 60% yield. Boc-Gly-L-Leu-OH was also used in the reaction to give product **6b** with a 74% yield. However, when Boc-L-Leu-Gly-OH was used as the dipeptide, **6c** was synthesized in a surprisingly low 33% yield. This low yield is likely due to competitive 1,6-HAT following radical formation,[26] which would yield a 3° radical that does not undergo addition to the allylic difluoride. Despite this, the reaction has proved to be viable with Boc-protected dipeptides.

We propose that the reaction mechanism follows a similar photocatalytic cycle as previously reported with *N*-alkylanilines,[20] although there is an inverted step sequence in which deprotonation must precede oxidation (**Scheme 6**). Indeed, in this system, the amino acid is first deprotonated by Na_2CO_3 to form the carboxylate intermediate **A**. This species is then oxidized by the excited iridium(III) photocatalyst to generate acyloxy radical **B**, which decarboxylates to form the α-aminoalkyl radical **C**. This reactive intermediate can then undergo regioselective addition to the terminal end of the electrophilic allylic difluoride, coupling the species together via C—C bond formation. Radical **D** is reduced to close the catalytic cycle and produce carbanion **E**, which readily undergoes an E1cB-like event to eject a fluoride ion and generate the monofluoroalkene-containing product. Contrary to our previous study, the acyclic products **4a-4f** favor



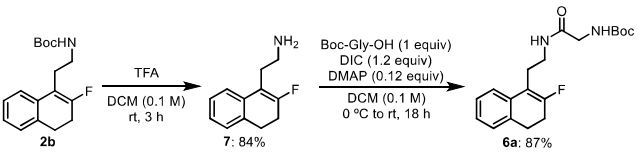
Scheme 5. 3-Fluoroallylation of Boc-protected dipeptides with allylic difluorides.



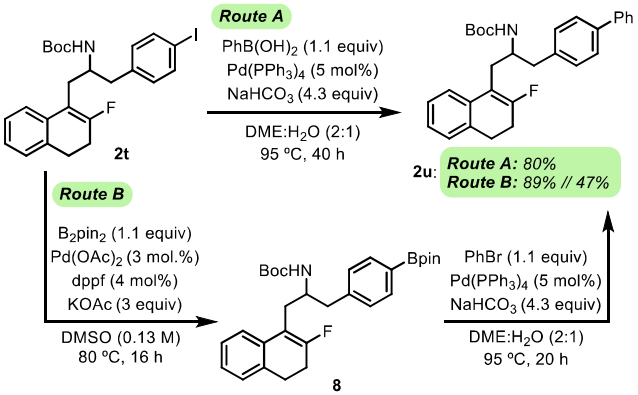
Scheme 6. Proposed reaction mechanism.

the *Z* isomer to a varying degree. We hypothesize that a conformational bias toward the pro-*Z* conformation is due to steric influences from the bulky Boc group and a preference for the minimization of gauche interactions.

Based on the impact monofluoroalkenes may have on peptide-based pharmaceuticals, we aimed to perform subsequent reactivity in the light of medicinal chemistry to demonstrate cases of post-functionalization. Our main focus was amide bond coupling (**Scheme 7**) and Suzuki–Miyaura cross-coupling reactions (**Scheme 8**), as these have been highlighted as two of the most impactful reactions in medicinal chemistry research.[27] First, we



Scheme 7. Amide bond coupling of compound **2b.**



Scheme 8. Suzuki–Miyaura cross coupling and Miyaura borylation of compound **2t**.

performed a Boc-deprotection on compound **2b** using trifluoroacetic acid at room temperature to synthesize the corresponding amine **7** with an 84% yield. This primary amine was then subjected to peptide bond coupling conditions (DIC, DMAP) with Boc-Gly-OH to produce amide **6a** with an excellent 87% yield. A Suzuki–Miyaura cross-coupling reaction was also performed between compound **2t** and phenylboronic acid in the presence of $Pd(PPh_3)_4$ and $NaHCO_3$ to give **2u** with an 80% yield. Alternatively, compound **2t** can be subjected to Miyaura borylation conditions with B_2pin_2 to synthesize the arylboronate ester **8** with an excellent 89% yield. Then, a Suzuki–Miyaura cross coupling can be performed, this time with bromobenzene, as a different route to product **2u** (47%) via swapping the roles of the reaction partners. The success of these reactions indicates the potential for late-stage functionalization toward medicinally relevant compounds.

3. Conclusion

In summary, we achieved the decarboxylative/defluorinative 3-fluoroallylation of α-amino acids with allylic difluorides. The product of these reactions contains a monofluoroalkene motif, which can be leveraged for medicinal chemistry research. The mild, photocatalytic conditions led to a broad reaction scope with excellent functional group tolerance, and the reaction can be performed with both cyclic and acyclic allylic difluorides. In the latter case, diastereomers are fully separable. The viability of different amine protecting groups beyond the Boc group was explored, and the reaction was also performed successfully with three Boc-protected dipeptides. In the interest of subsequent reactivity, examples of amide bond formation, Suzuki–Miyaura cross-coupling and Miyaura borylation reactions were achieved, highlighting the potential for late-stage functionalization. Further decarboxylative radical processes are currently being investigated in our group to expand the library of precursors for photocatalytic C—C bond formation leading to fluorinated products.

4. Experimental Section

General Procedure for the Photocatalytic 3-Fluoroallylation Reaction

Under nitrogen, a 4-mL vial affixed with a rubber septum was charged with the protected amino acid or dipepetide (0.360 mmol, 1.2 equiv), followed by Na_2CO_3 (0.600 mmol, 2 equiv) and 1.5 mL of dry DMF. The solution was stirred for 15 min to allow for full deprotonation of the carboxylic acid. $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (0.006 mmol, 2 mol%) was then added to the reaction mixture. A solution of allylic difluoride (0.300 mmol, 1 equiv) in dry DMF (1.5 mL) was added to the reaction mixture, the 4-mL vial was sealed with a Teflon-lined cap, and the reaction mixture was irradiated with LED lights (465 nm, 3.5 W) for 18–72 h. Water was added, the reaction mixture was extracted with ethyl acetate (×2), and the combined organic layers were washed with water (×3) and brine. The organic solution was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The product was purified by flash chromatography.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: allylic difluorides · amino acids · C—C coupling · monofluoroalkenes · photocatalysis

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