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Difluoromethylheteroarylation of unactivated alkenes through remote heteroaryl migration with bis(difluoroacetyl) peroxide

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ABSTRACT

We have developed a straightforward method for synthesizing distal difluoromethyl-substituted ketones bearing heteroaryl groups. This approach utilizes difluoromethylheteroarylation of unactivated alkenes through remote heteroaryl migration by employing bis(difluoroacetyl) peroxide (generated in situ from DFAA and urea·H_2O_2) as the difluoromethylating agent. Sunlight was proved to promote this transformation.

Introduction

The incorporation of fluorine atoms or fluorine-containing substituents into agrochemicals, pharmaceuticals, and biomaterials has been shown to enhance their efficacy. This modification is now widely recognized as a means to alter a compound's chemical, biological, and physical properties [1]. For instance, the difluoromethyl group has been demonstrated to confer unique modifications on biological activities [2], including its role as a more lipophilic H-bond donor compared to groups such as OH, NH, or SH [3]. Consequently, significant efforts have been directed toward introducing difluoromethyl groups into organic molecules. Among these strategies, the difunctionalization of alkenes stands out as a highly effective method for the simultaneous introduction of two functional groups into a molecule [4].

In recent years, difluoromethyl radical-mediated difunctionalization of alkenes via intramolecular functional group migration has emerged as a highly effective protocol for the synthesis of diverse difluoromethylated ketones [5]. Notably, substantial progress has been achieved in radical difluoromethylation of distal formyl, imino, and heteroaryl groups, enabling efficient access to a wide range of difluoromethyl-functionalized aldehydes, imines, and heteroarenes [6]. In 2019, Wang and colleagues reported a photocatalytic difluoroalkylation-distal functionalization of unactivated alkenes using *N*-(2,2-difluoroacetoxy) benzimidoyl chloride, under the catalysis of Ir[{dF(CF_3)ppy}$_2$(dtbbpy)] PF_6 and B(OPh)$_3$ (Scheme 1, equation a) [7]. Subsequently, the same group developed an electrochemically promoted difluoroalkylation-distal functionalization of unactivated alkenes with HCF_2SO_2Na (Scheme 1, equation b) [8]. In 2021, Wang and Cai achieved a semi-heterogeneous photocatalytic difluoroalkylation-distal heteroaryl migration of unactivated alkenes with HCF_2SO_2Na by employing CN-K as the photocatalyst (Scheme 1, equation c) [9]. Then, in 2022, Zhou and colleagues realized a visible-light-mediated Iridium-catalyzed difluoromethylarylation of unactivated alkenes via a (hetero)aryl neophyl-like radical migration (Scheme 1, equation d) [10].

However, the aforementioned methods often rely on either expensive iridium photocatalysts or costly difluoromethyl sources. Beyond conventional difluoromethyl radical precursors, such as HCF_2SO_2Na, bromodifluoromethyltriphenyl phosphonium bromide, (Het) $ArSO_2CF_2H$, N-tosyl-*S*-difluoromethyl-*S*-phenylsulfoximine, 2-(difluoromethyl)-2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one and PhI$(OCOCHF_2)_2$, [11] difluoroacetic anhydride (DFAA) has emerged as a readily available and economical alternative for difluoromethyl radical generation, following the pioneering work of Sodeoka in 2023 (Scheme 1, equation e) [12]. Building on this, our group reported in 2024 a photochemical difluoromethylation of quinoxalin-2(1*H*)-ones using DFAA and pyridine *N*-oxide (Scheme 1, equation f) [13]. Herein, we extended this methodology to achieve difluoromethyl heteroarylation of unactivated alkenes via remote heteroaryl migration, utilizing bis (difluoroacetyl) peroxide as difluormethylation reagent which was generated in situ from the combination of DFAA and urea·H_2O_2 (Scheme 1, equation g).

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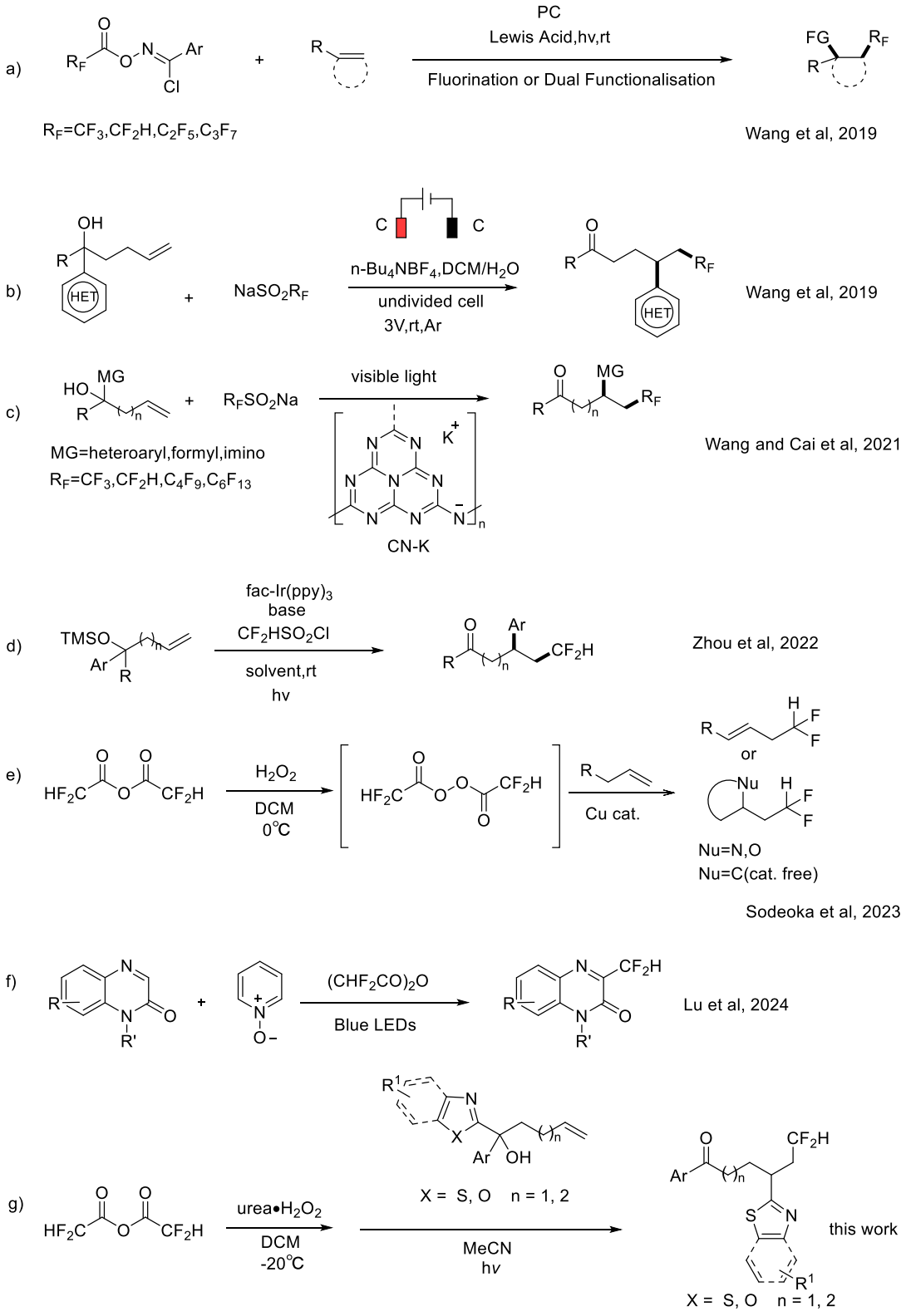
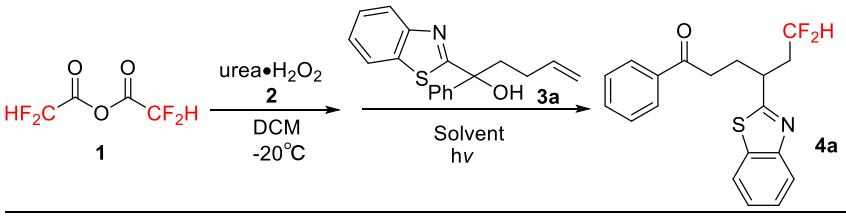
Results and discussion

We initially selected 1-(benzod*d*thiazol-2-yl)-1-phenylpent-4-en-1-ol (**3a**) as a model substrate to optimize reaction conditions. In situ generated bis(difluoroacetyl) peroxide (BDFAP) was prepared from 17.7 equivalents of difluoroacetic acid anhydride (DFAA) and 2.4 equivalents of urea·H_2O_2 in dichloromethane (DCM) at −20 °C. The reaction mixture was then exposed to sunlight and stirred at room temperature for 2.5 h, affording the difluoromethylation-distal heteroaryl migration product **4a** in 71 % yield (Table 1, entry 1). Notably, under dark conditions, the yield dropped to 64 %, indicating that light catalyzes the decomposition of BDFAP to difluoromethyl radicals (Table 1, entry 2). To further



Scheme 1. Difluoromethylation-distal heteroaryl migration of unactivated alkenes.

Table 1
Optimization of reaction conditions.[a]



Entry	**1**/equiv	**2**/equiv	Solvent (mL)	Yield (%)[b]
1	17.7	2.4	DCM (1.5)	71
2	17.7	2.4	DCM (1.5)	64[c]
3	17.7	2.4	DCE (1.5)	74
4	17.7	2.4	MeCN (1.5)	76
5	17.7	2.4	THF (1.5)	71
6	17.7	2.4	DMAc (1.5)	74
7	17.7	2.4	NMP (1.5)	75
8	17.7	2.4	DMSO (1.5)	trace
9	17.7	2.4	toluene (1.5)	70
10	17.7	2.4	1,4-dioxane (1.5)	69
11	17.7	2.4	MeOH (1.5)	trace
12	17.7	2.4	DMF (1.5)	73
13	15.0	2.4	MeCN (1.5)	70
14	17.7	2.4	MeCN (1.0)	68
15	17.7	2.4	MeCN (2.0)	72
16	17.7	2.4	MeCN (1.5)	80[d]
17	17.7	2.4	MeCN (1.5)	79[e]
18	17.7	2.4	MeCN (1.5)	79[f]

[a] Reaction conditions: **1** (4.5–5.31 mmol) and **2** (0.72 mmol) were mixed in DCM (0.5 mL) at −20 °C for 1 h, then **3a** (0.30 mmol) and solvent (1.0–2.0 mL) was added under argon and the mixture was stirred under sunshine for 2.5 h at r.t.
[b] Isolated yields.
[c] The reaction was carried out in dark.
[d] The reaction mixture was stirred for 3 h.
[e] The reaction was carried out under the irradiation of 3 W white LEDs.
[f] The reaction mixture was stirred for 8 h.

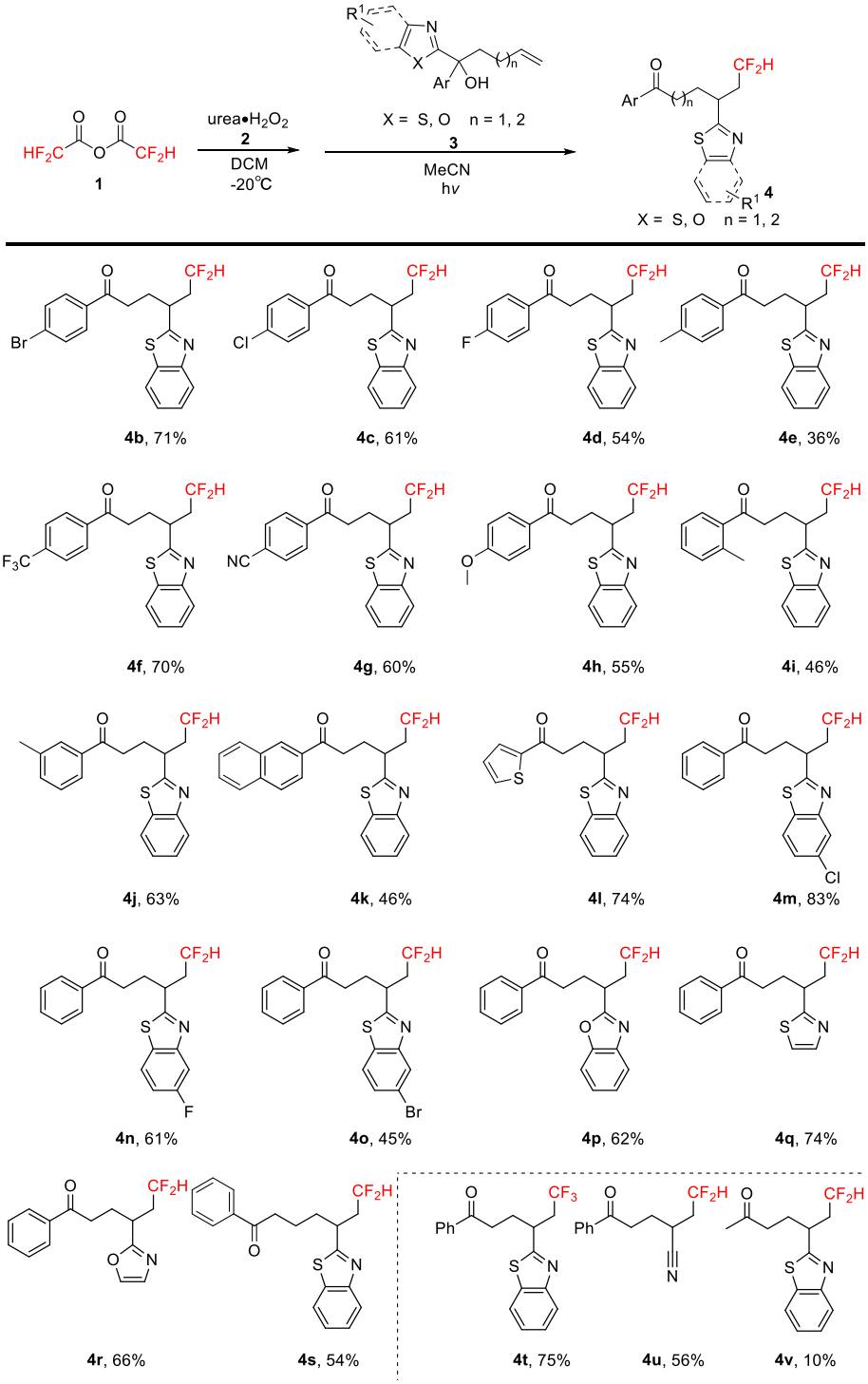
improve the yield, various solvents were evaluated, including 1,2-dichloroethane (DCE), acetonitrile (MeCN), tetrahydrofuran (THF), *N*,*N*-dimethylacetamide (DMAc), *N*-methylpyrrolidone (NMP), dimethyl sulfoxide (DMSO), toluene, 1,4-dioxane, methanol, and *N*,*N*-dimethylformamide (DMF). MeCN was identified as the optimal solvent (Table 1, entries 3–12). Subsequently, the loading of BDFAP and the concentration of **3a** were optimized. Reducing the DFAA equivalent to 15 equivalents resulted in a slightly lower yield of 70 % (Table 1, entry 13). Increasing the concentration of **3a** to 0.30 M or decreasing it to 0.15 M also resulted in decreased yields (Table 1, entries 14 and 15). Finally, extending the reaction time to 3 h increased the yield to 80 %, while further prolongation to 8 h had no significant effect on the yield (Table 1, entries 16 and 18). Notably, when the reaction was carried out under the irradiation of 3 W white LEDs, the desired product was obtained in 79 % yield (Table 1, entry 17). Thus, the optimal reaction conditions were determined as follows: **1** (5.31 mmol), **2** (0.72 mmol) in DCM (0.5 mL) at −20 °C for 1 h, then **3a** (0.30 mmol) in MeCN (1.5 mL) was added and stirred under sunshine for 3 h at room temperature.

After optimizing the reaction conditions, the substrate scope was investigated (Scheme 2). The benzothiazolyl group exhibited excellent migratory selectivity, regardless of whether electron-donating or electron-withdrawing substituents were present on the phenyl ring of tertiary alcohols **3**. Furthermore, both naphthyl-substituted and thienyl-substituted benzothiazole–tertiary alcohol derivatives proceeded smoothly to afford the corresponding migration products **4k** and **4l** in 46 % and 74 % yields, respectively. Halogen-substituted benzothiazole–tertiary alcohols, as well as those bearing benzoxazole, thiazole, or oxazole groups, were also well tolerated, furnishing the desired products (**4m**–**4r**) in moderate to good yields. Of particular note, treatment of 1-(benzo[*d*]thiazol-2-yl)-1-phenylhex-5-en-1-ol (**3s**) yielded the target migration product **4s** in 54 % yield. To further expand the substrate scope, trifluoroacetic anhydride (TFAA) was employed as an alternative to difluoroacetic anhydride (DFAA). Encouragingly, the reaction smoothly afforded the trifluoromethyl-distal heteroaryl migration product **4t** in 75 % yield. Additionally, the cyano group was identified as an effective migration group, delivering the desired product **4u** in 56 % yield. Notably, when 2-(benzo[*d*]thiazol-2-yl)hex-5-en-2-ol (**3u**) was used as substrate, the desired product **4v** in 10 % yield. When 1-(oxazol-2-yl)-1-phenylbut-3-en-1-ol (**3v**) (n = 0), 1-(benzo[*d*]thiazol-2-yl)-1-phenylhept-6-en-1-ol (**3w**) (n = 3), and 1-(benzo[*d*]thiazol-2-yl)-1-phenyloct-7-en-1-ol (**3×**) (n = 4) were used as substrates, no desired product was obtained.

To investigate the reaction mechanism, two control experiments were conducted. When di-tert-butylhydroxytoluene (BHT, 17.7 equiv) or ethene-1,1-diyldibenzene (17.7 equiv) was added to the reaction mixture under the optimized conditions, no desired product was detected. Instead, the BHT radical adduct (**5**) and ethene-1,1-diyldibenzene adduct (**6**) was observed by GC–MS. These results suggest that the reaction proceeds via a radical mechanism (Scheme 3).

According to the literature and our experimental observations, a proposed mechanism is illustrated in Scheme 4. The reaction is initiated by the in situ generation of BDFAP from DAFF and urea·H_2O_2, which subsequently undergoes fragmentation (with or without light irradiation) to generate the difluoromethyl radical. This radical then adds to compound **3a**, affording radical species **7**, which undergoes intramolecular addition to the heteroaryl group to form radical intermediate **8**. Following this, ring-opening of intermediate **8** occurs, yielding a more stable radical species **9**. Finally, species **9** undergoes oxidation and deprotonation to give product **4a**.

Finally, a 5.0 mmol scale reaction of **3a** was carrried out to illustrate the practical application. To our delight, 1.35 g desired product **4a** was obtained in 77 % yield (Scheme 5). Notably, when the large scale reaciton was carried out in dark, the yield dropped to 67 %. These results demonstrated that sunlight exposure could promote this reaction.



Scheme 2. Substrate scope.

Conclusion

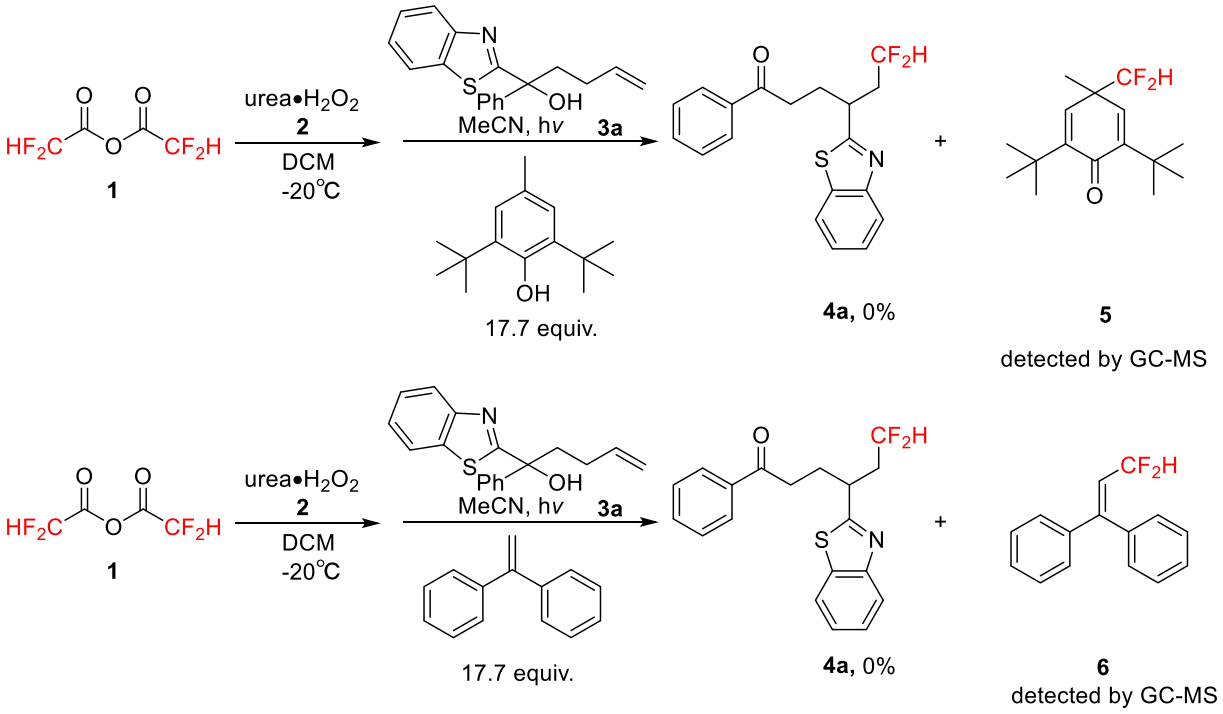
In summary, we have developed a difluoromethyl migration-based heteroarylation protocol for unactivated alkenes, utilizing bis(difluoroacetyl) peroxide as the difluoromethylating agent, which is generated in situ from the combination of DFAA and urea·H_2O_2. Notably, sunlight was identified as an effective promoter for this transformation. The mild and metal-free reaction conditions highlight the protocol's utility as a convenient and environmentally benign synthetic approach for accessing distal difluoromethyl-substituted ketones.

CRediT authorship contribution statement

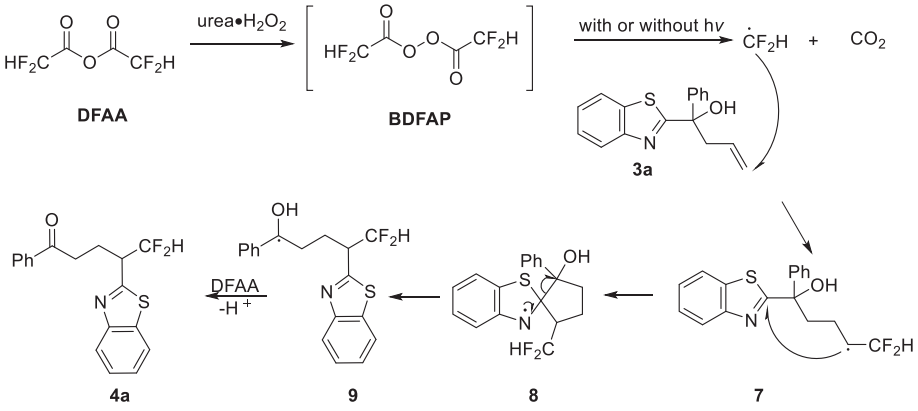
Zhiqi Lei: Writing – original draft, Investigation, Data curation. **Xiaoyu Wang:** Investigation, Data curation. **Siqi Li:** Validation, Investigation. **Xia Zhao:** Writing – review & editing, Supervision, Conceptualization. **Kui Lu:** Writing – review & editing, Supervision.

Declaration of competing interest

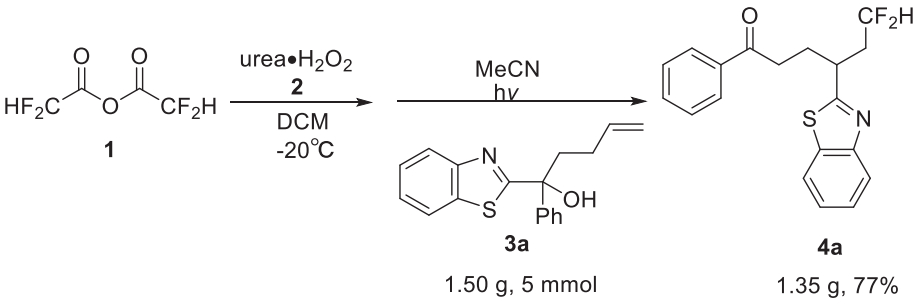
The authors declare that they have no known competing financial



Scheme 3. Radical inhibition and trapping experiment.



Scheme 4. Possible reaction mechanism.



Scheme 5. Scale up of this reaction.

interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2025.155842.

Data availability

Data will be made available on request.

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