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Photocatalytic *In Situ* Amination of the Migrating Aryl Group: Rapid Access to 4-Aminated Benzenepropanamides

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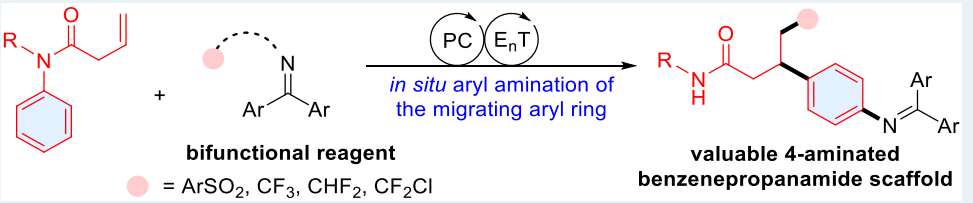

ABSTRACT: Aryl migration-induced difunctionalization of alkenes is a fascinating strategy for increasing the molecular complexity via the simultaneous formation of two chemical bonds across the C−C double bond. Despite the significant advances in this area, the *in situ* functionalization of the migrating aryl ring remains elusive due to the incompatibility between the conventional arene C−H functionalization strategy and the aryl migration process. Herein, we disclose the photocatalytic *in situ* amination of the migrating aryl ring in which an aryl ring is aminated and migrated within a single step, providing rapid access to valuable 4-aminated benzenepropanamide scaffolds. Such transformations enable the formation of an additional chemical bond on the migrating aryl ring beyond those two formed on the alkene carbons, significantly increasing the flexibility of the aryl migration strategy and improving the migration efficiency for the aminated aryl ring. The energy transfer catalytic cycle between the photosensitizer and the bifunctional reagents plays a pivotal role in combining the aryl migration process with the emerging radical-based arene remote C−H amination step. Experimental mechanistic studies support the proposed reaction pathway. The power of this protocol was demonstrated by the functionalization of pharmaceutically relevant molecules, the efficient synthesis of bioactive molecule analogs, and antibacterial activity investigations.

KEYWORDS: *aryl migration, radical amination, alkene difunctionalization, 4-aminated benzenepropanamide, antibacterial activity*

INTRODUCTION

The 4-aminated benzenepropanamide skeleton was designed as a core pharmacophore exhibiting antitumor,[1] antileukemic,[2] and antivirus activities, such as dengue and West Nile virus.[3] For instance, several representative 4-aminated benzenepropanamide moiety-containing molecules with diverse bioactivities are shown in Figure 1a.[4−7] Thus, the development of mild and reliable synthetic methods for the efficient construction of such skeletons is highly sought after.

Aryl migration-mediated difunctionalization[8−17] of alkenes represents one of the most straightforward strategies for rapid access to benzenepropanamide skeletons from commodity alkenes (Figure 1b, left).[18−21] The aryl migrations generally start from the reaction of preprepared aryl group-tethered alkenes with *in situ* generated radical species, followed by an aryl migration process, enabling the migration of the preinstalled aryl group. In terms of certain desired aryl groups, the preinstallation process can sometimes be synthetically complex or prohibitively difficult, which restricts the generality of this strategy. Significant advances have been made to increase the flexibility of this strategy and improve the migration efficiency of a specific aryl group.[22−28] For instance, Stephenson and co-workers disclosed the photocatalytic aminoarylation of alkenes, enabling the efficient installation of various aryl groups to the alkenes by simply selecting different arylsulfonylacetamides as bifunctional reagents.[26,29] Zhu and co-workers reported the aryl difluoromethylation of alkenes via a novel docking-migration strategy, in which the migrating aryl group is involved in the dual-function reagent.[23,24,28] Later, Studer et al. disclosed an unprecedented B-to-C aryl migration strategy, enabling the flexible variation of the migrating aryl group by an *in situ* tethering strategy.[27] While these seminal strategies significantly improve the migration efficiency of a specific aryl group, the requirement for prepreparation of the bifunctional reagents and the utility of strong basic and nucleophilic aryl lithium reagents limit their applications to some degree.

Direct arene C−H functionalization offers the most efficient strategy for constructing substituted aromatic compounds, and

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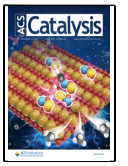

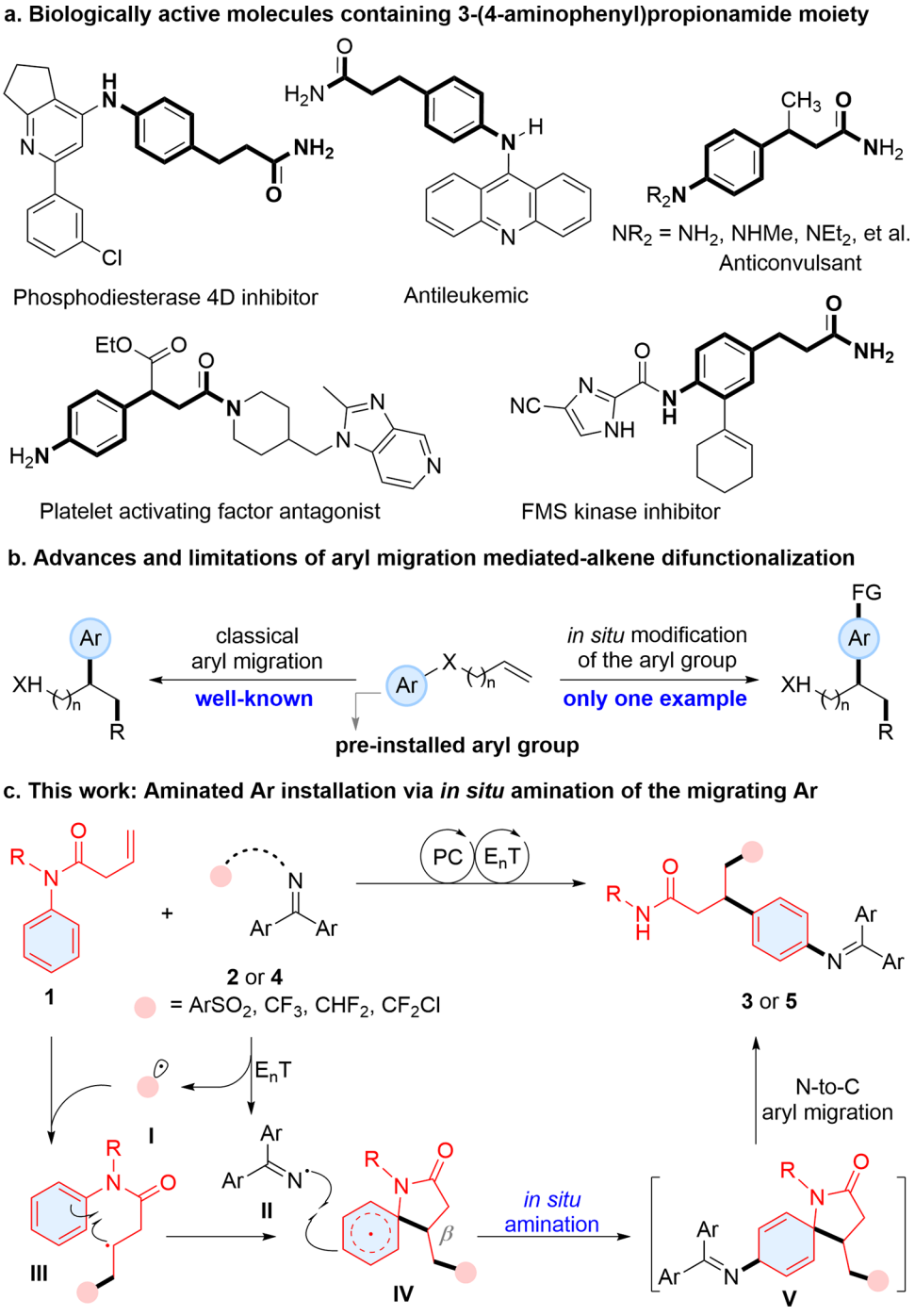

Figure 1. Backgrounds and design of installation of aminated aryl rings via *in situ* amination of the migrating aryl rings.

substantial advances have been achieved.[30] Nonetheless, the *in situ* functionalization of a migrating aryl group during the migration process remains elusive, presumably due to the incompatibility between the conventional metal-catalyzed arene C−H functionalization and the radical-based aryl migration process (Figure 1b, right). Most recently, our group and Li group independently developed a conceptually new radical-mediated arene remote C−H functionalization strategy, which has been successfully applied in *para*-selective arene amination[31] and acylation.[32,33] This emerging radical-based arene C−H amination strategy may be compatible with the aryl migration process, providing an opportunity to realize the amination of the migrating aryl ring.[34] Herein, we report a photocatalytic aryl migration strategy for the efficient synthesis of 4-aminated benzenepropanamide skeletons via *in situ* amination of the migrating aryl group (Figure 1c). The simultaneous photocatalytic generation of two radical species with distinct reactivity, a persistent one and a transient one, plays a pivotal role in combining the aryl migration process with the arene remote C−H amination step. The transient radical species (**I**) and the persistent iminal radical (**II**)[35−42] separately dominate the radical addition with the C−C double bond (**1** to **III**) and the subsequent *in situ* amination process (**IV** to **V**). The cleavage of the inert C−N bond finally finishes the migration of the 4-aminated aryl ring, delivering the valuable 4-aminated benzenepropanamide skeleton. The

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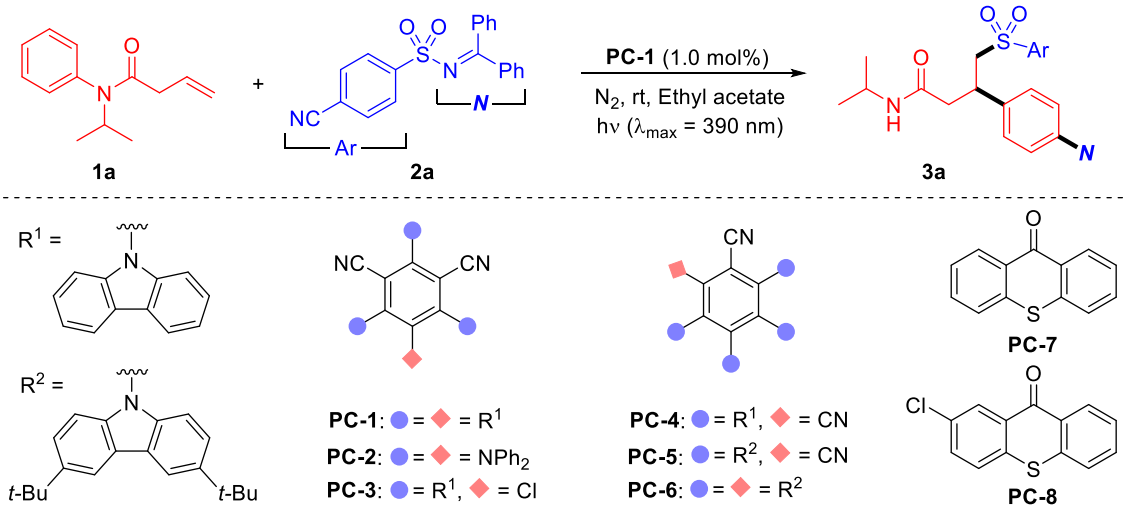
Table 1. Optimization of the Reaction Conditions[a]



entry	variation of the reaction conditions	**3a** [%][b]
1	none	20
2	**PC-2** instead of **PC-1**	18
3	**PC-3** instead of **PC-1**	10
4	**PC-4** instead of **PC-1**	5
5	**PC-5** instead of **PC-1**	18
6	**PC-6** instead of **PC-1**	54
7	**PC-6**, **1a**: **2a** = 1:1.8	56
8	**PC-6**, λ_{max} = 400 nm	45
9	**PC-6**, λ_{max} = 427 nm	28
10	**PC-7** instead of **PC-1**	58
11	**PC-8** instead of **PC-1**	64
12	As entry 11, methyl acetate or DCM as a solvent	61
13	As entry 11, THF or MeCN as a solvent	40, 46
14	As entry 11, DMF as a solvent	trace
15	As entry 11, **PC-8** (0.5 mol %) instead of **PC-8** (1.0 mol %)	64
16	As entry 11, **PC-8** (0.5 mol %), extend the reaction time to 10 h	71 (68[c])
17	without **PC**	0

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), **PC** (1.0 mol %), and solvent (2 mL) were irradiated in 390 nm LED light for 6 h under N_2 atmosphere, 30∼40 °C. [b]Yield determined by NMR using 1,1,2,2-tetrachloroethane as the internal standard. [c]Isolated yield.

reaction features the *in situ* amination of the migrating aryl ring, circumventing the tedious synthetic route for preparing substrates that bear an amino group at the *para*-position. The structure of the obtained benzenepropanamides can be varied by simply selecting different bifunctional reagents. The reaction was successfully applied in the functionalization of pharmaceutically relevant molecules, the efficient divergent synthesis of bioactive molecule analogs, and antibacterial activity investigations. Experimental studies support the proposed reaction pathway.

RESULTS AND DISCUSSION

Reaction Optimization. To pursue our hypothesis, a suitable bifunctional reagent that enables the generation of both a transient radical (participation in the radical addition step, **I** to **III**) and a persistent nitrogen radical species (dominating the radical recombination step, **IV** to **V**) should be selected. Sulfonyl imines have emerged as powerful reagents for simultaneously generating sulfonyl radicals and iminyl radicals via the homolysis of the weak N−S bond (≈70 kcal/mol) under photocatalytic energy transfer (EnT) process.[43−47] Thus, sulfonyl imine **2a** (1.5 equiv) was selected as the model bifunctional reagent to react with a C−C double bond-tethered *N*-phenyl amide **1a** (1.0 equiv). Preliminary attempt using 4CzIPN (1 mol %) as a photosensitizer, together with ethyl acetate as the solvent, under light irradiation (λ_{max} = 390 nm) affords the desired benzenepropanamide **3a** in 20% yield (Table 1, entry 1). Subsequent examination of several cyanobenzene-derived photosensitizers such as **PC-2** − **PC-5** failed to improve the reaction yield (entries 2−5). Interestingly, pentacarbazole cyanobenzene **PC-6** exhibited high catalytic efficiency, with **3a** obtained in 54% yield. Increasing the amount of **2a** to 1.8 equiv provides a slightly improved yield (entry 7). Lights with longer wavelengths lead to dropped yields (entries 8−9). Considering the high triplet state energy of thioxanthone (65.5 kcal/mol)[48] and its capability to act as an efficient energy transfer agent, thioxanthones **PC-7** and **PC-8** were used to catalyze the current transformation. To our delight, the use of 2-chlorothioxanthone **PC-8** as the photosensitizer provides a 64% yield of **3a**. Solvent screening demonstrated that both methyl acetate and DCM gave comparable yields to ethyl acetate (entry 12), THF and MeCN led to remarkable drops in yields (entry 13), and strong polar solvent DMF is unsuitable as a reaction mediator (entry 14). A reduced catalyst loading (0.5 mol %) gave maintainable

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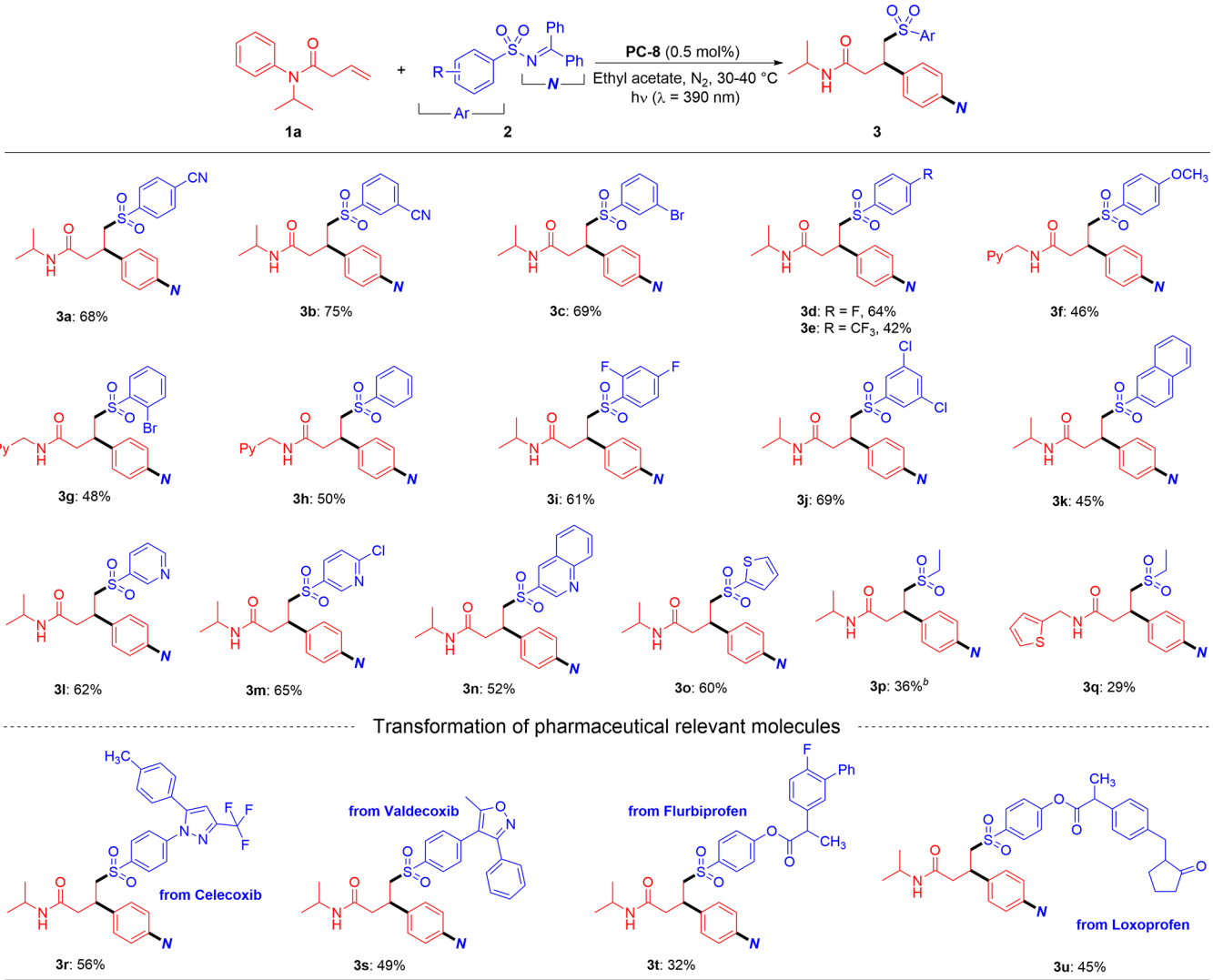
Table 2. Substrate Scope of Bifunctional Reagent Sulfonyl Imines[a]



[a]Reaction conditions: **1** (0.1 mmol), **2** (0.15 mmol), **PC-8** (0.5 mol %), and EtOAc (2 mL) were irradiated in 390 nm LED light for 10 h under N_2 atmosphere, 30∼40 °C. [b]Reaction is conducted in the presence of **PC-8** (5 mol %) for 15 h.

yield (entry 15). Extending the reaction time from 6 to 10 h further improves the yield to 71%, with the corresponding isolated yield being 68% (entry 16). At last, the control experiment demonstrated that the photosensitizer was crucial for this reaction, as the transformation was suppressed entirely without the presence of the **PC-8** (entry 17).

Substrate Scope. After identifying the optimal reaction conditions, we turned our attention to investigating the generality of the current photocatalytic amination/migration transformations. The scope of the sulfonyl imine **2** was first investigated with amide **1a** as the model reaction partner (Table 2). The reactions exhibit broad functional group tolerance for the sulfonyl imines regardless of the electronic effect. For instance, electron-withdrawing groups such as cyano (**3a**), fluorine atom (**3d**), and trifluoromethyl (**3e**) at the *para*-position of the sulfonyl imines proceeded with the reaction smoothly, affording the corresponding aminated benzenepropanamides in moderate to good yields. Cyano and bromine at the *meta*-position were well tolerated, giving **3b** and **3c** in 75 and 69% yields, respectively. Strong electron-donation methoxyl group at the *para*-position leads to only slight erosion of the yield, with **3f** isolated in 46% yield. The steric effect on the sulfonyl group has little impact on the reaction outcome. For instance, sulfonyl imine bearing a bromine atom adjacent to the sulfonyl radical center proceeded the reaction smoothly, with the product **3g** obtained in a slightly decreased yield. Dihalogenated sulfonyl imines such as 2,4-difluoro and 3,5-dichloro sulfonyl imines were successfully rearranged to the corresponding benzenepropanamides **3i** and **3j** in 61 and 69% yields, respectively. The halogen atoms in these molecules provide opportunities for further functionalization reactions. Heterocycles are a ubiquitous feature of pharmaceuticals and agrochemicals, and their introduction into organic molecules therefore attracts significant attention.[49,50] Fortunately, heteroaromatic sulfonyl imines, including those bearing pyridine ring (**3l** & **3m**), quinoline ring (**3n**), and thiophene ring (**3o**), were well tolerated, with the corresponding heterocycle containing targets obtained in 52−65% yields, respectively. The aliphatic sulfonyl radicals generally undergo a quick desulfuration process to generate alkyl radical species, posing a significant challenge for the radical addition of aliphatic sulfonyl radicals to alkenes. Nonetheless, the ethanesulfonyl imine was a

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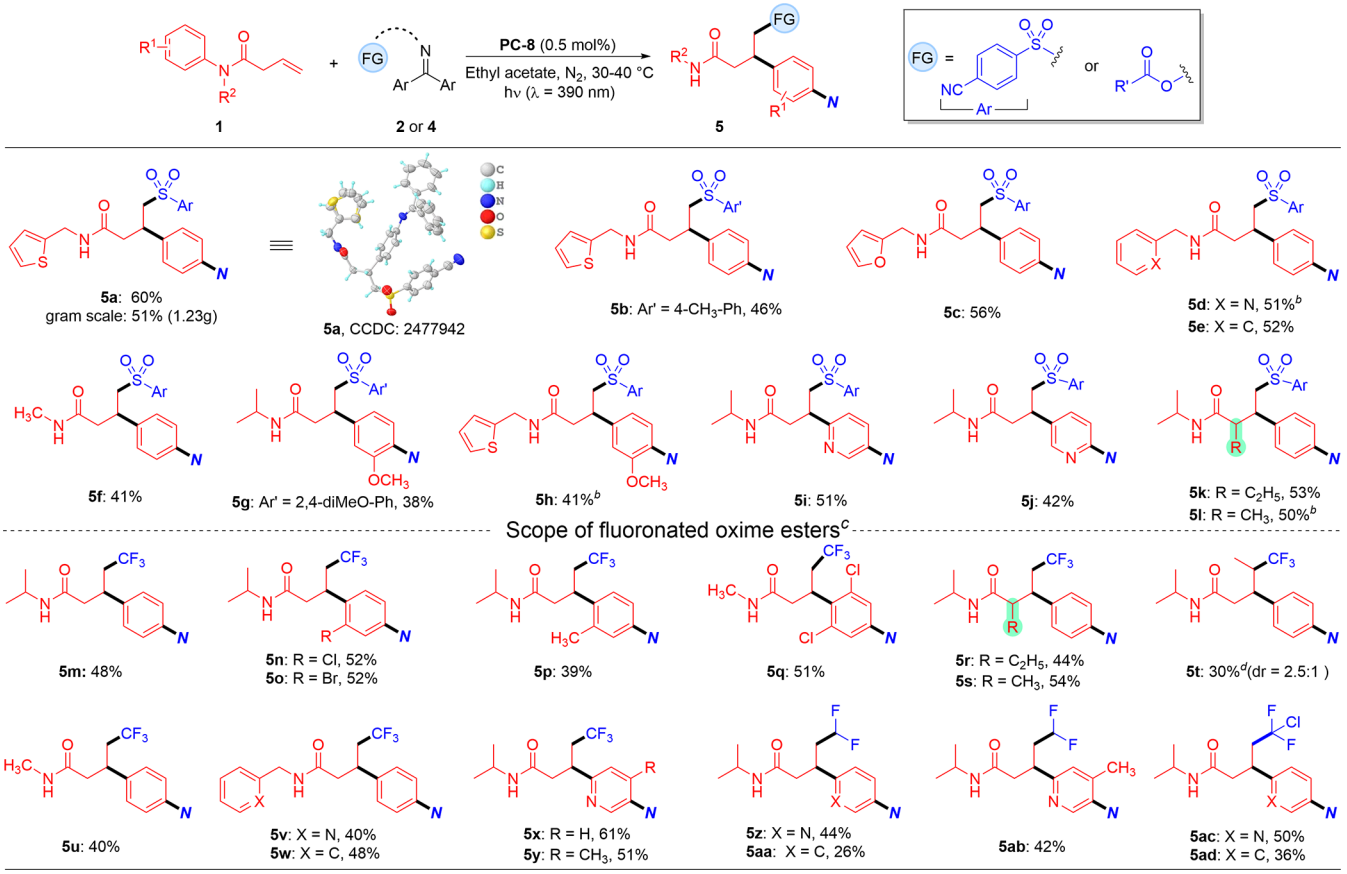
Table 3. Substrate Scope of the Amides and Oxime Esters[a]



[a]Reaction conditions: **1** (0.1 mmol), **2** (0.15 mmol), **PC-8** (0.5 mol %), and EtOAc (2 mL) were irradiated in 390 nm LED light for 10 h under N_2 atmosphere, 30~40 °C. [b]Reaction is conducted in the presence of **PC-8** (5 mol %) for 15 h. [c]Reaction conditions: **1** (0.1 mmol), **4** (0.18 mmol), **PC-8** (5 mol %), and EtOAc (2 mL) were irradiated in 390 nm LED light for 8 h under N_2 atmosphere. [d]Reaction conditions: **1** (0.1 mmol), **4** (0.2 mmol), **PC-8** (10 mol %), and EtOAc (2 mL) were irradiated in 390 nm LED light for 6 h under N_2 atmosphere.

competent bifunctional reagent for the current transformations, albeit with remarkably dropped yields (**3p** & **3q**).

To test the practical utility of our strategy, several pharmaceutical-relevant molecules were submitted to the standard conditions. Specifically, the sulfonyl amine moiety-containing drugs Celecoxib and Valdecoxib were converted into the sulfonyl imines and submitted to our reactions, affording the corresponding products in 56% (**3r**) and 49% (**3s**) yields, respectively. Indeed, the current reactions enable the deaminative tethering of the sulfonamides to the valuable 4-aminated benzenepropanamides, providing quick access to prepare related hybrid drugs. Flurbiprofen- and Loxoprofen-derived sulfonyl imines were also competent substrates, albeit with slightly low yields (**3t** & **3u**).

We subsequently explored the generality of the current reaction for *β,γ*-unsaturated carboxylic amide **1** with sulfonyl imine **2a** as the model reaction partners (Table 3). Initially, the relatively bulky isopropyl group was believed to facilitate amide **1a** adopting a geometrically favorable conformation for the radical cyclization step. Thus, the generality of other nitrogen protecting groups (R^2) was first investigated. Switching the isopropyl to a thiophen-2-ylmethyl group resulted in the formation of **5a** and **5b** in 60% and 46% yields, respectively. The structure of **5a** was further confirmed by the X-ray diffraction analysis of its single crystal (CCDC: 2477942). To demonstrate the potential application of the current reactions, the production of **5a** was scaled up to a gram scale, with **5a** isolated in comparable yield. Other protecting groups, such as furan-2-ylmethyl (**5c**), pyridin-2-ylmethyl (**5d**), benzyl (**5e**), and methyl (**5f**), are all tolerated, with the corresponding products obtained in acceptable to moderate yields. Appropriately increasing the catalyst loading and extending the reaction time can slightly improve the yield of **5d** (51%). The substituent on the *N*-protecting phenyl ring exhibits a significant influence on the current reaction regardless of its electronic effect. Among many of the tested *ortho*- or *meta*-substituents, only the aryl group bearing a methoxyl group at the *meta*-position gave acceptable yields (**5g** and **5h**). This phenomenon may be attributed to the steric and electronic influences of the substituents on the cyclization and the subsequent radical recombination steps. The reaction was successfully applied to the migration and functionalization of a pyridine ring. Interestingly, two disubstituted pyridine compounds with reversed substituent positions (**5i** and **5j**) can be obtained by using different starting materials. Substituent at the *α* position of the *β,γ*-unsaturated amide has little influence on the reaction, as the ethyl- and methyl-containing products (**5k** and **5l**) are obtained in 53 and 50% yields, respectively. The introduction of fluoroalkyl motifs into target organic molecules has long been a topic of interest in synthetic, medical, and materials science due to the unique properties induced by fluorine and fluoroalkyl.[51,52] Thus, we

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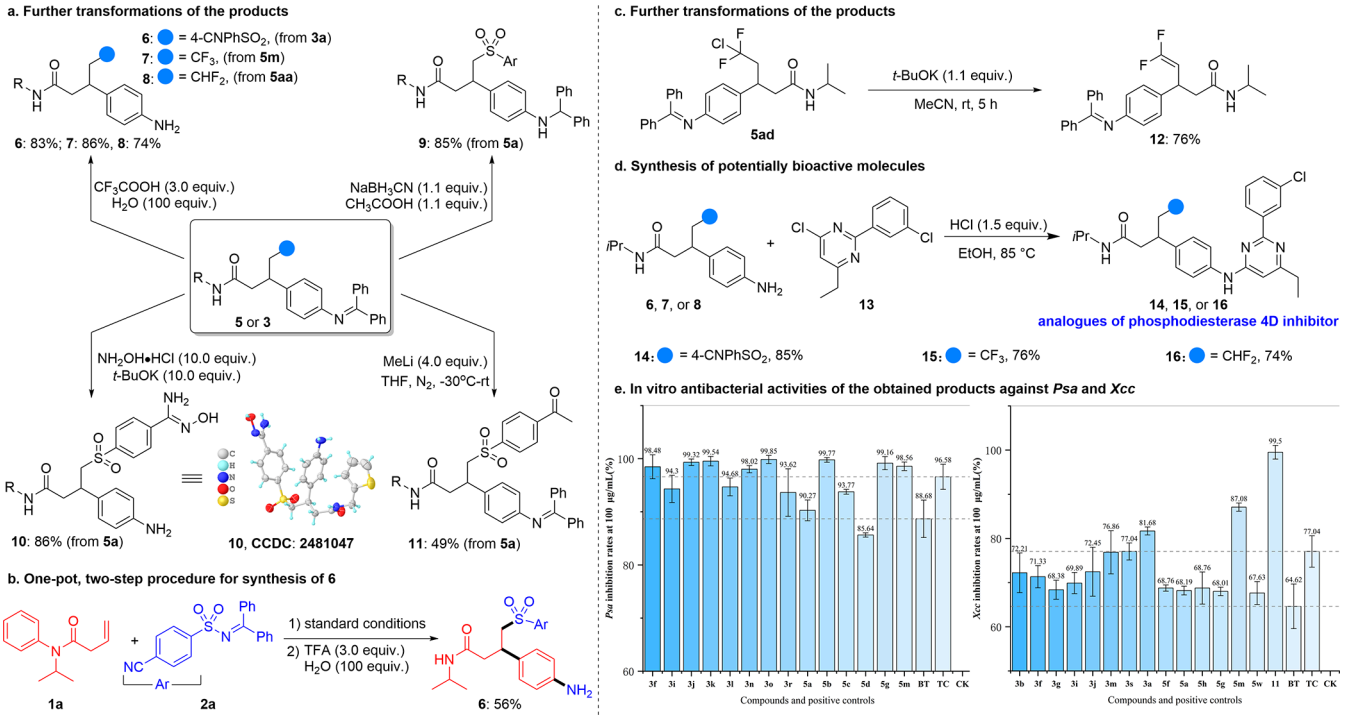
Scheme 1. Practical Applications of the Current Reaction



attempted to extend the current strategy to trifluoromethyl/arylation of the alkenes for preparing fluoroalkyl motif-containing aminated phenylpropanylamides. Recently, oxime esters have emerged as powerful bifunctional reagents for vicinal difunctionalization of alkenes via a triplet energy transfer process.[39−42,53,54] Our group has also reported the *para*-selective amination of arenes using benzyl alcohol-derived oxime esters.[31] Inspired by these seminal works, trifluoroacetyl oxime **4a** was selected as the bifunctional reagent to react with amide **1a**. To our delight, the reaction proceeded successfully to afford the trifluoromethyl-containing target in 48% yield (**5m**). The current trifluoromethyl/arylation of alkene exhibits better tolerance for the substituents on the amide's aryl ring. For instance, amides bearing a chlorine/bromine atom or a methyl group adjacent to the spiro carbon proceeded the reaction smoothly, affording the corresponding aminated phenylpropanylamides in 52% (**5n**), 52% (**5o**), and 39% (**5p**) yields, respectively. Particularly, the 2,6-dichloro aniline-derived amide, which poses significant steric hindrance for the spiro cyclization step, was also an effective substrate, affording desired product **5q** in 51% yield. Both α- and γ-substituted amides are competent substrates, successfully providing the corresponding targets (**5r−5t**). The relatively low yield of **5t** may be attributed to the steric effect of methyl on the radical addition or radical cyclization steps. Besides, oxime esters derived from other fluorine atom-containing acids, such as difluoroacetic acid and chlorodifluoroacetic acid, proved to be effective substrates, providing access to preparing difluoromethyl- or chlorodifluoromethyl-containing phenylpropanylamides (**5z-5ad**).

Applications. The products contain multiple functional groups for diverse further transformations. For instance, the imine group can be converted into an amino group in the presence of trifluoroacetic acid, producing valuable sulfonyl, trifluoromethyl, or difluoromethyl group-containing 4-amino phenylpropylamides **6−8** in 83, 86, and 74% yields, respectively. To further enhance the practicality of our method, a one-pot, two-step procedure that integrates the aryl migration and hydrolysis steps was conducted using **1a** as the starting material (Scheme 1b). The desired product **6** was obtained in 56% yield, which is consistent with the yield of the two-step operation. Additionally, the imine group can be converted to a secondary amine moiety via the reduction of the C−N double bond by $NaBH_3CN$, producing **9** in 85% yield. The cyano group in compound **5a** can react with hydroxylamine hydrochloride in the presence of equal equivalents of potassium *tert*-butoxide as a base to produce (*Z*)-*N*′-hydroxybenzimidamide **10** in 86% yield. Simultaneously, the imine group in **5a** was converted to the amino group. The structure of compound **10** was further confirmed by X-ray diffraction analysis of the corresponding single crystal (CCDC: 2481047). The cyano group can also react with nucleophiles such as methyllithium, producing ketone product **11** in 49% yield. Treatment of **5ad** by *t*-BuOK (1.1 equiv) in MeCN at room temperature for 5 h leads to the elimination of hydrogen chloride, delivering valuable gem-difluoroalkene **12** in 76% yield (Scheme 1c). Considering the wide application of the 3-(4-aminophenyl)propionamide moiety in bioactive molecules,[4−7] we applied our reaction in the divergent synthesis of several analogues of phosphodiesterase 4D inhibitor. Reacting the above-obtained anilines **6−8** with preprepared chlorinated pyrimidine **13** in the presence of 1.5 equiv of hydrogen chloride resulted in the formation of sulfonyl, trifluoromethyl, or difluoromethyl-containing potential bioactive molecules in 85% (**14**), 76% (**15**), and 74% (**16**) yields, respectively (Scheme 1d).

As part of our continuous interest in designing and preparing structurally innovative small molecules with biological activity in agricultural applications,[55−57] the antibacterial activity against *Xanthomonas campestris* pv. *campestrisis* (*Xcc*) and *Pseudomonas syingae* pv. *actinidiae* (*Psa*) of the obtained 3-(4-aminophenyl)propionamides was evaluated, with commercial

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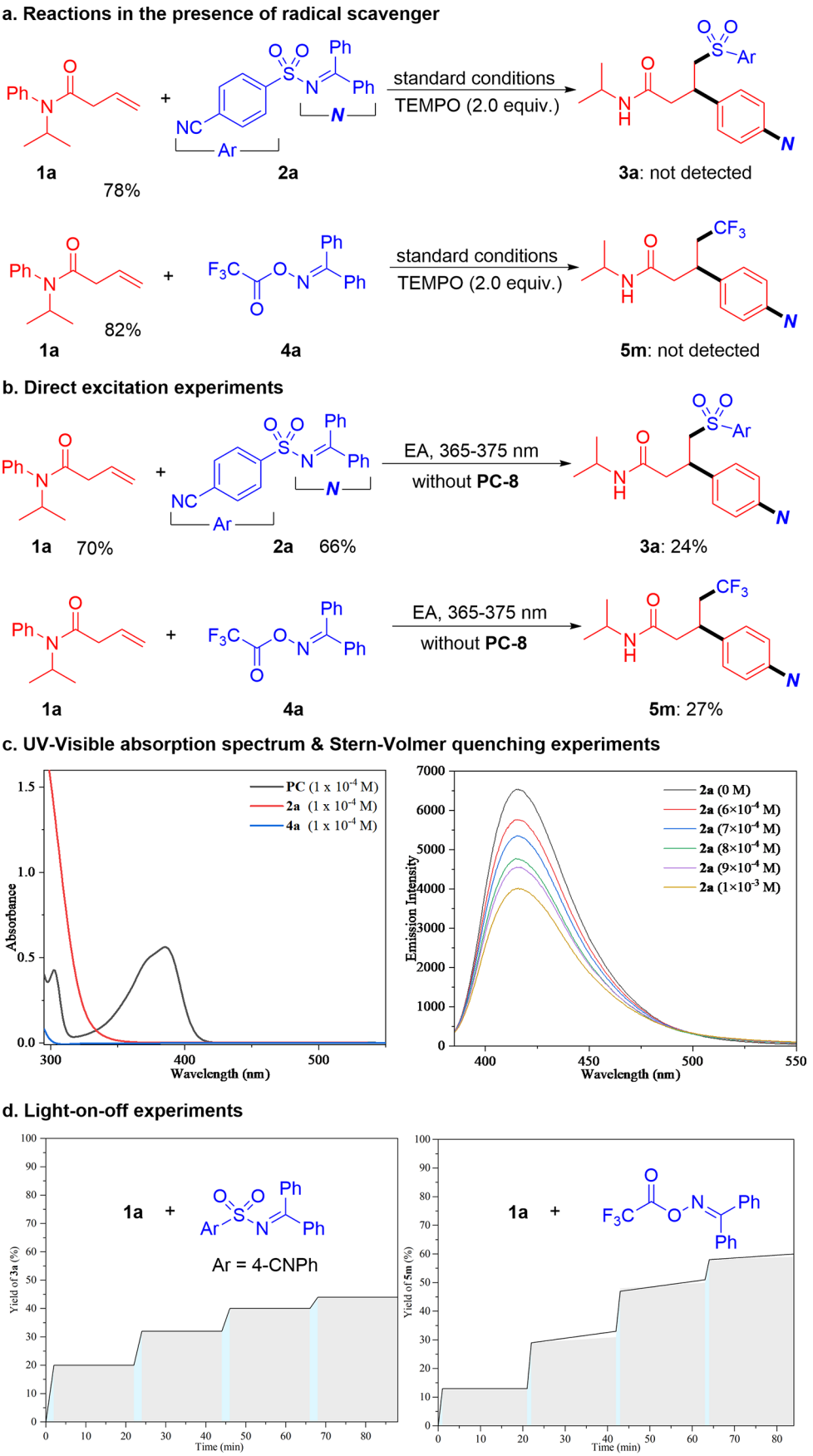

Figure 2. Mechanistic studies.

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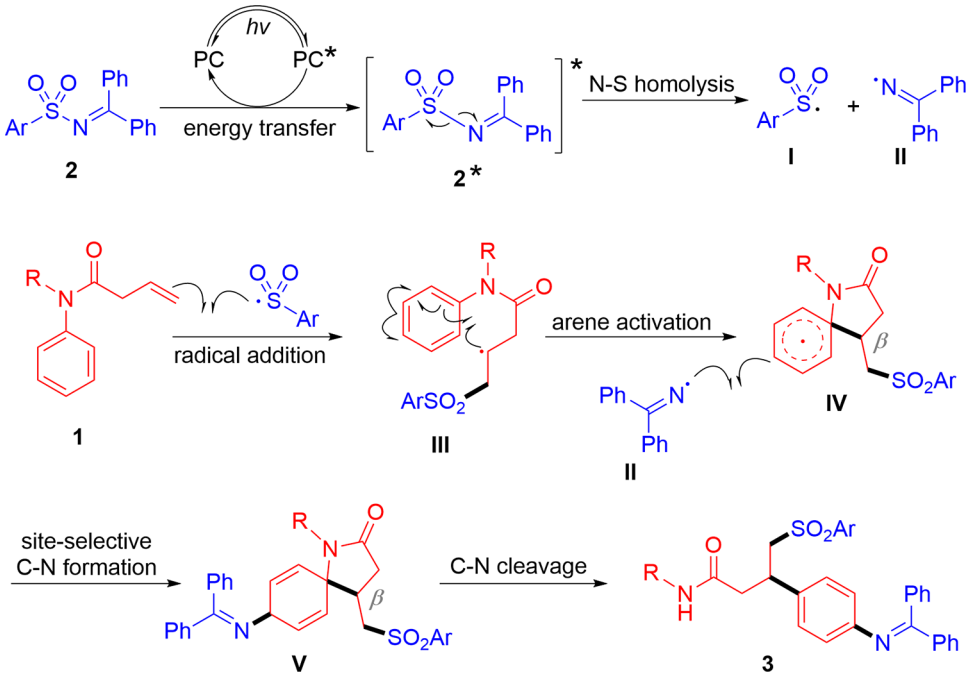
Scheme 2. Possible Reaction Pathway



bactericides bismerthiazol (BT) and thiodiazole copper (TC) used as positive controls. As shown in Scheme 1e, most of the tested products exhibited excellent inhibitory activity against *Psa* at 100 μg/mL, surpassing commercial bactericides BT and TC (Scheme 1e, left). The antibacterial activity against *Xcc* at 100 μg/mL also gave impressive results (Scheme 1e, right). The high inhibitory rates demonstrate that our products have the potential to be developed as new bactericides for crop protection.

Mechanistic Studies. Multiple experimental studies were conducted to gain insight into the reaction pathway (Figure 2). First of all, TEMPO was added to the model reactions as a radical scavenger under otherwise identical conditions (Figure 2a). As a result, both the arylsulfonylation and trifluoromethylarylation reactions were suppressed entirely, suggesting the radical character of the current reactions. Reactions that proceed through the triplet state of substrates should be feasible through direct light excitation, which distinguishes them from reactions through a single-electron transfer pathway. Thus, the model reactions were conducted under short-wavelength light (λ = 365−375 nm) without the presence of **PC-8** as a photosensitizer (Figure 2b). As expected, the desired **3a** and **5m** were successfully obtained, albeit with remarkably dropped yields, confirming the energy transfer pathway. The UV−visible absorption data revealed that only **PC-8** has absorption at 390 nm (Figure 2c, left). The matched triplet state energy of thioxanthone-type catalyst and sulfonyl imines[43] and oxime esters favors the energy transfer process between the **PC-8** and the bifunctional reagents. To confirm this conclusion, sulfonyl imine **2a** was selected as the example to conduct the Stern−Volmer quenching experiments with **PC-8**. As depicted in Figure 2c, the emission of **PC-8** can be effectively quenched by the sulfonyl imine **2a**. At last, light on−off experiments revealed that the sulfonyl imine and oxime ester involved reactions behave differently in the dark. Specifically, the slightly increased yield in the oxime ester reaction supports the involvement of a radical chain pathway (Figure 2d). In contrast, no reaction occurs in the sulfonyl imine reaction, even in a prolonged time in the dark (Figure 2d). Nonetheless, this is not sufficient to rule out a chain propagation mechanism, since the radical chain is likely to decay too fast to be detected on a laboratory time scale.[58,59]

Based on the above experimental studies and reported literature,[31−33] a possible reaction pathway was proposed and described in Scheme 2 using sulfonyl imine as a representative example. The reaction begins with light excitation of the photosensitizer and subsequent energy transfer with sulfonyl imine **2**, affording excited state **2***, which undergoes N−S bond homolysis to generate sulfonyl radical **I** and iminyl radical **II**. Radical addition of sulfonyl radical **I** to the C−C double bond of amide **1** leads to the formation of aryl ring tethered carbon radical **III**. Intramolecular radical *ispo*-addition to the aryl ring leads to the ultraremote activation of the arene's *para*-position, generating the spiro cyclic intermediate **IV**. Subsequent site-selective radical recombination enables the formation of a new C−N bond at the *para*-position of the aryl ring, delivering a spiro cyclohexadiene **V**. The specific site selectivity of such radical recombination step has been rationalized in our previously reported arene remote functionalizations.[31,33] At last, intermediate **V** undergoes an energy barrierless rearomatization step via cleavage of the old C−N bond to produce the final 4-aminated phenylpropylamine **3**.

CONCLUSIONS

In summary, we have developed a photocatalytic aryl migration-mediated difunctionalization of alkenes for rapid access to valuable 4-aminated benzenepropanamide skeletons. The reaction features the *in situ* formation of the 4-aminated aryl rings via radical-based remote arene C−H amination, which significantly enhances the flexibility of the classical aryl migration strategy and improves the migration efficiency of the 4-aminated aryl group. The reactions are suitable for several different bifunctional reagents, enabling the divergent synthesis

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of sulfonyl-, trifluoromethyl-, difluoromethyl-, or chlorodifluoromethyl-containing benzenepropanylamides in moderate to good yields. The practical utility of the current strategy is demonstrated by late-stage modification of pharmaceutical-relevant molecules, further transformation of the products, synthesis of potentially bioactive molecules, and antibacterial activity investigations. Experimental mechanistic studies support our proposed reaction pathway. We believe that the current strategy will bring new ideas for designing novel aryl migration-based synthetic methods and expedite the synthesis of complex structures.

METHODS

General Procedure for the Photocatalytic Aryl Amination/Migration Transformation. To a 10 mL Schlenk tube equipped with a stir bar was added unsaturated amide **1a** (20.3 mg, 0.10 mmol), sulfonyl ketimines **2a** (52.0 mg, 0.15 mmol), and **PC-8** (0.2 mL in ethyl acetate, 2.5 mM). The Schlenk tube was sealed and placed under argon before 1.8 mL of dry ethyl acetate was added. The reaction was stirred and irradiated with two LED Kessil lamps (λ_{max} = 390 nm, intensity = 100%, 3 cm away from the Schlenk tube, with a cooling fan to keep the reaction temperature at 30∼40 °C) for 10 h. The reaction mixture was then concentrated under vacuum to afford the crude material, which was purified by column chromatography (silica gel, PE/EtOAc) to give product **3a**.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.5c06638.

Experiment procedures and characterization of all new compounds and X-ray structure data of compounds **5a** & **10** (PDF)

5a (CIF)

10 (CIF)

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Author Contributions

D.C. performed main methodology development, scope evaluation, and synthetic application; T.T., T.L., and D.L. contributed to earlier studies; S.-C.R. and Y.R.C. conceptualized and directed the project and drafted the manuscript with assistance from all coauthors. All authors contributed to part of the experiments and/or discussions.

Notes

The authors declare no competing financial interest.

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