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Catalytic three-component carboamination of unactivated alkenes with primary sulfonamides

A novel photocatalytic radical carboamination of unactivated alkenes, employing simple primary sulphonamides, has been showcased. This approach pioneers the synthesis of a broad range of nitrogen-rich molecular architectures through the formation of both carbon–nitrogen and carbon–carbon bonds. Notably, this innovative method displays exceptional compatibility with a vast array of functional groups, emphasizing its high efficiency in modifying complex drug molecules and natural products in exceedingly mild conditions during post-synthetic stages.

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Catalytic three-component carboamination of unactivated alkenes with primary sulfonamides†

Ying Zhang,  Kai-Dian Li,  Chang-Quan Zhou,  Zhi-Xi Xing and Huan-Ming Huang  *

Catalytic multicomponent reactions offer an efficient synthetic approach for constructing multiple chemical bonds in a single step. However, the carboamination of unactivated alkenes, involving nitrogen radical species directly from N–H precursors, is infrequent due to the high bond energy and challenges in step matching. Herein we demonstrate a catalytic radical three-component reaction using simple primary sulfonamides, which provides a novel method for constructing a library of complex architectures through carbon–nitrogen and carbon–carbon bond formation. The newly developed method demonstrates a high degree of tolerance towards various functional groups, proving to be highly efficient in the late-stage modification of complex drug molecules and natural products under very mild conditions.

Introduction

The ability to design sustainable and atom-economical synthetic transformations always creates a revolution in organic synthesis.¹ Catalytic multicomponent reactions (MCRs) are very powerful synthetic methods in the construction of carbon–carbon and carbon–heteroatom bonds to generate complex architectures in a single reaction vessel.² Radical cross-couplings have emerged as valuable methods for forming C(sp³)–C(sp³) and C(sp³)–X bonds under mild conditions, driven by advancements in transition-metal catalysis,³ photoredox chemistry⁴ and electrosynthesis.⁵ Recently, nitrogen-centered radicals (NCRs) have proven to be versatile reactive intermediates, successfully employed in multicomponent reactions (MCRs) for the generation of nitrogen-containing motifs. This achievement has been realized through suitable excited photocatalysts⁶ or electrochemical conditions.^{5c} Nevertheless, pre-functionalization of nitrogen-based precursors is consistently required, often involving multiple steps.^{6,7}

Remarkably, Knowles,⁸ Rovis⁹ and others⁶ developed elegant examples regarding remote C–H functionalization triggered by nitrogen centered radical species generated from the N–H bonds directly (Scheme 1A). Intramolecular and intermolecular hydroamination of unactivated alkenes represent another powerful synthetic transformation for constructing nitrogen-containing motifs.¹⁰ For example, Knowles and co-

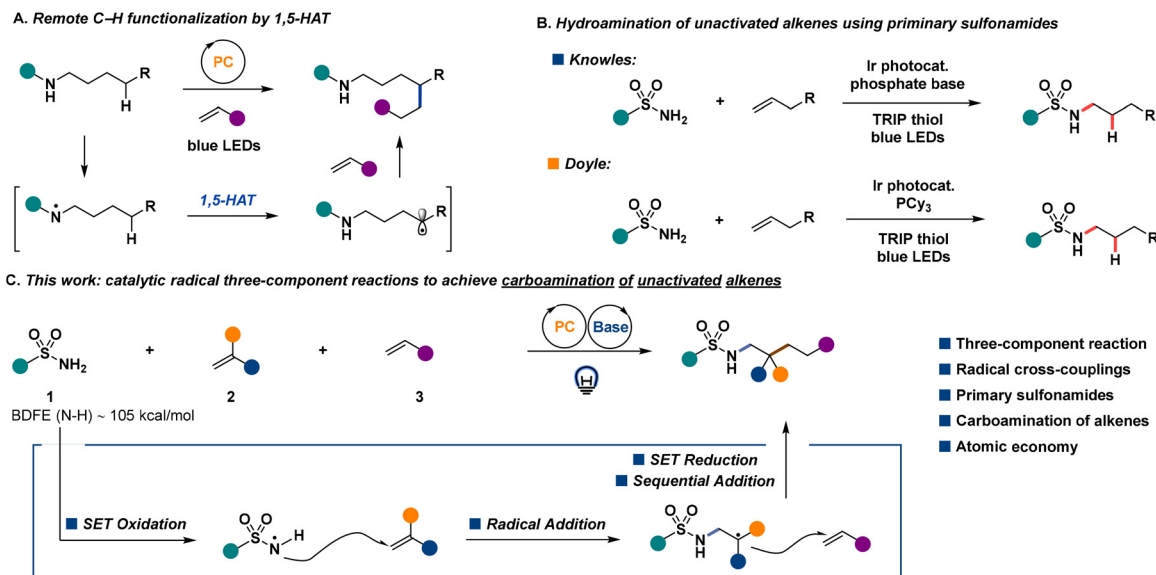
workers achieved the intermolecular anti-Markovnikov hydroamination of unactivated alkenes with sulfonamide through a proton coupled electron transfer (PCET)¹¹ approach (Scheme 1B, up).¹² Doyle and her team utilized a catalytic amount of phosphine and photocatalysis to achieve hydroamination of unactivated alkenes with primary sulfonamides *via* α -scission from phosphoranyl radicals (Scheme 1B, down).^{13a} Additionally, Knowles,^{10c} Molander,^{13b} Moeller,^{13c} Qin,^{13d} Xu,^{13e} Nevado,^{13f} Ohmiya,^{13g} and others⁶ also achieved intramolecular cascade reaction triggered nitrogen centered radical intermediates directly generated from N–H bonds. However, these valuable transformations primarily focus on remote C–H functionalization, intramolecular cyclization and hydroamination (Scheme 1A and B). Although several noteworthy efforts have been made, including those of Scheidt^{14a} and Xia & Yang,^{14b} the direct generation of nitrogen-centered radicals (NCRs) from N–H bonds, followed by their participation in catalytic multicomponent reactions (MCRs), is still rare due to the high bond dissociation free energy (BDFE) associated with N–H bonds.^{12,13a} Furthermore, the control of radical intermediates and the sequential achievement of fundamental radical addition/coupling steps in multicomponent reactions (MCRs) pose significant challenges.

Herein, we envisioned that the N–H bond of primary sulfonamides (BDFE ~ 105 kcal mol^{−1}, $E_{1/2} = +2.6$ V *versus* SCE in MeCN)^{12,13a} could be converted to the corresponding nitrogen centered radical, and then sequential radical addition steps could be controlled by polar effects (Scheme 1C).¹⁵ The catalytic three-component carboamination reactions between primary sulfonamides and olefins offer a sustainable method for synthesizing secondary sulfonamide derivatives. These reactions achieve a remarkable 100% atom utilization

School of Physical Science and Technology, ShanghaiTech University, Shanghai 201210, China. E-mail: huanghm@shanghaitech.edu.cn

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Scheme 1 Background and our design.

Table 1 Reaction optimization^a

Entry	Deviation from standard conditions	Yield ^b %	Entry	Deviation from standard conditions	Yield ^b %
1	Condition A	0	10	MeCN as solvent	65
2	Condition B	0	11	2 mol% Ir–F was used	78
3	Ir–F (4 mol%), K ₂ CO ₃ (2 equiv.) as base and PhCF ₃ : <i>t</i> BuOH = 1 : 1 (0.2 M) as solvent	0	12	1a : 2a : 3a = 1.5 : 2 : 1 was used	85 (82) ^c
4	Ir–F (4 mol%), K ₃ CO ₄ (2 equiv.) as base and PhCF ₃ : <i>t</i> BuOH = 1 : 1 (0.2 M) as solvent	17	13	12 h	69
5	Ir–F (4 mol%), K ₃ CO ₄ (40 mol%) as base and PhCF ₃ : <i>t</i> BuOH = 1 : 1 (0.2 M) as solvent	67	14	48 h	80
6	None	88 (84) ^c	15	4-CzIPN as photocatalyst	<5
7	<i>t</i> BuOH as solvent	63	16	Ru(bpy) ₃ (PF ₆) ₂ as photocatalyst	<5
8	PhCl as solvent	65	17	Na ₃ PO ₄ /Cs ₂ CO ₃ /[2.4.6]-collidine/ K ₂ HPO ₄ as base	6/80/29/ 36
9	DCM as solvent	73	18	PhCF ₃ (0.4 M)	83
			19	PhCF ₃ (0.1 M)	84
			20	No base/photocatalyst/light/50 °C	0/0/0/0

Ir-F

X-ray crystal structure of 4

Condition A
Ir[dF(CF₃)ppy]₂(4,4'-d(CF₃)-bpy)PF₆ (2 mol%) as PC
TBAOP(O)(O*i*Bu)₂ (20 mol%) as base
PhCF₃ (0.2 M) as solvent

Condition B
Ir-F (2 mol%) as PC
2,4-Lutidine (10 mol%) as base
PCy₃ (2.5 mol%) as addition
PhCF₃ (0.2 M) as solvent

^a Optimization of the reaction conditions: 1a (0.2 mmol, 1.0 equiv.), 2a (0.4 mmol, 2.0 equiv.), 3a (0.4 mmol, 2.0 equiv.), Ir–F (4 mol%), and K₃PO₄ (40 mol%) in PhCF₃ (1.0 mL, 0.2 M) at room temperature under irradiation with 30 W blue LEDs with a cooling fan for 24 hours. ^b Yields determined by ¹H NMR with nitromethane as an internal standard. ^c Yields of the isolated product.

efficiency, making them environmentally friendly. This approach clearly showcases its green credentials by minimizing the *E*-factor and maximizing atom economy, thereby

demonstrating the environmental benefits of the current method.¹⁶ These derivatives are versatile motifs found in bio-active molecules and drugs.¹⁷



Results and discussion

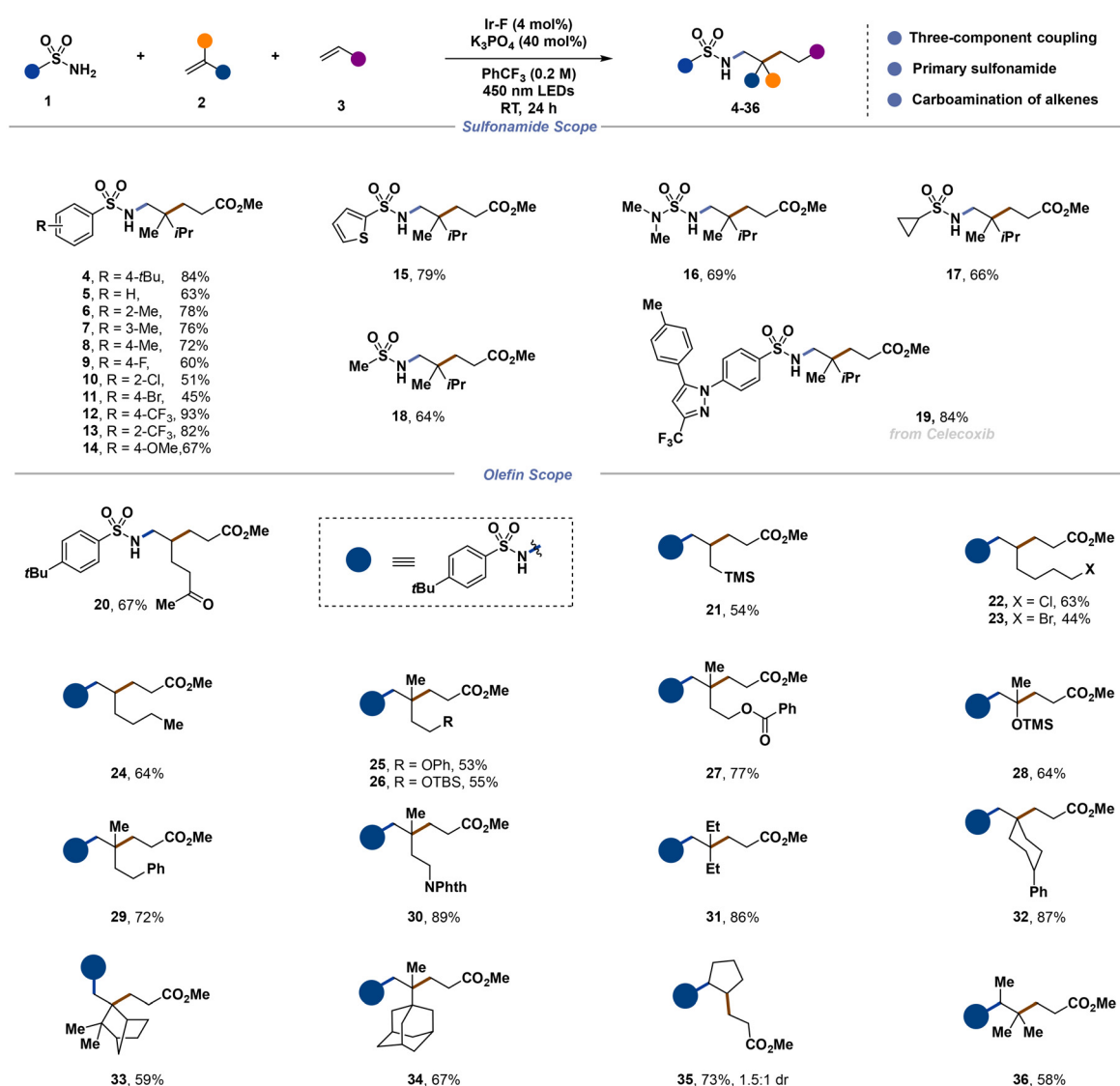
Optimization

With these considerations in mind, we started to investigate this three-component carboamination reaction by employing primary sulfonamide **1a**, unactivated olefin **2a** and methyl acrylate **3a** under visible light conditions (Table 1). Unfortunately, the desired product **4** could not be formed under either condition A (entry 1)^{12a} or condition B (entry 2).^{13a} Additionally, the coupling product **4** also could not be generated with 4 mol% Ir-F and 2 equivalents of K₂CO₃ with mixture solvent (PCF₃ : tBuOH = 1 : 1, 0.2 M, entry 3) as previously applied in the synthesis of cyclic amines by our group.¹⁸ Pleasingly, the coupling product **4** could be formed in 17% yield with K₃PO₄ as a base instead of K₂CO₃ (entry 4). X-ray crystallographic analysis confirmed the structure of product **4**.¹⁸ Interestingly, the yield of **4** increased dramatically to 67% when a catalytic amount of

K₃PO₄ was used (entry 5). With a catalytic amount of iridium based photoredox catalyst (Ir-F) and K₃PO₄, the desired coupling product **4** could be obtained in 84% isolated yield (entry 6) using PhCF₃ as reaction solvent. Then, different solvents (entries 7–10) were also investigated, and we did not observe any better results. Despite efforts to decrease the loading of the photoredox catalyst or alter the amounts of coupling partners or change the reaction time or use different photocatalysts or different bases, the yield of product **4** did not increase (entries 11–19). Finally, we demonstrated that the base, photocatalyst, and visible light were necessary to achieve this three-component coupling reaction successfully (entry 20).

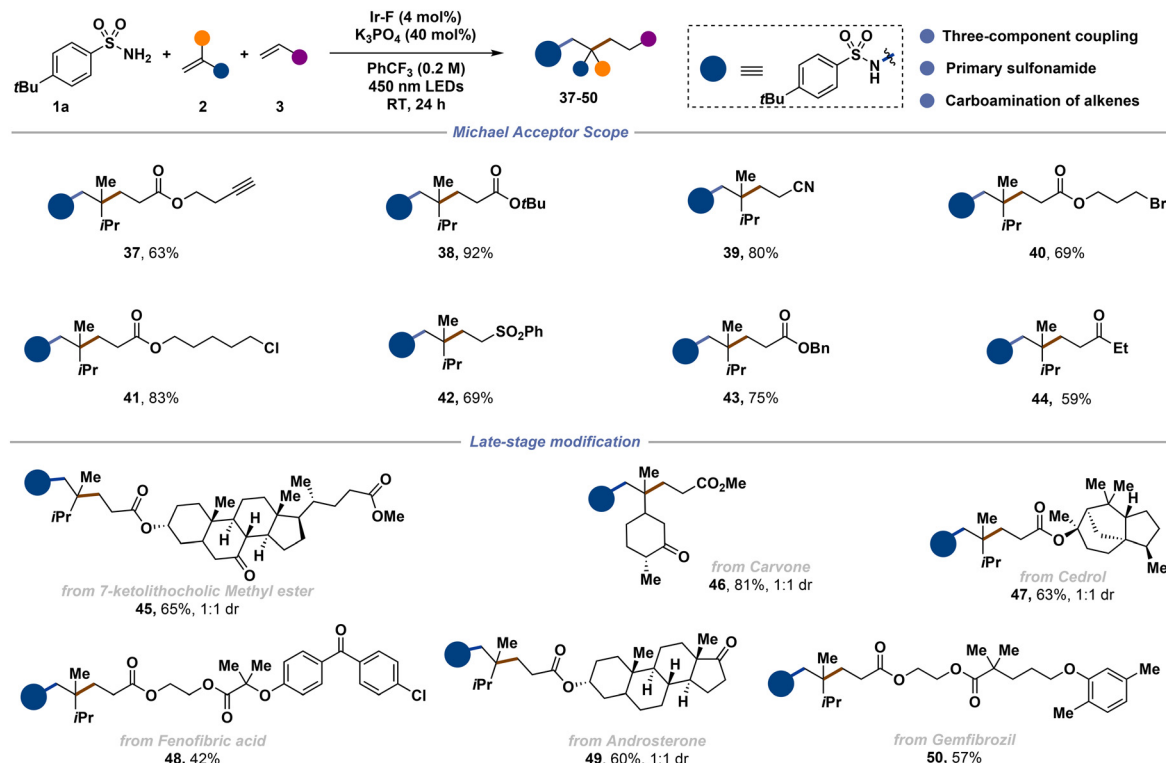
Reaction scope

Have established the reaction conditions, we started to investigate the primary sulfonamide scope of catalytic radical three-component reactions (Scheme 2). The aromatic ring with



Scheme 2 Sulfonamide and olefin scope of catalytic radical three-component reactions.





Scheme 3 Michael acceptor scope and late-stage modification of catalytic radical three-component reactions.

various substituents, such as alkyl, fluoride, chloride, bromide, trifluoromethyl, and methoxyl could be tolerated with good to excellent yields (4–14). Additionally, thiophene (15), amine (16), cyclopropyl (17), methyl (18) and the anti-inflammatory drug celecoxib (19) were also compatible under the current reaction conditions, and the desired products 15–19 could be produced in 64%–84% isolated yields. Unfortunately, secondary sulfonamide was not compatible in our catalytic system. Furthermore, different unactivated olefins were also screened, mono-substituted olefins containing ketone (20), silicon (21), halide (22 and 23), and alkyl (24) functional groups were all tolerated with moderate to excellent yields. We then examined a variety of functional groups in the 1,2-disubstituted olefin component including ether (25), diverse protecting groups (26 and 28), ester (27), phenyl (29), phthalimide (30), diethyl (31), and carbocycles (32–34). The further results of inner olefins (35 and 36) also showed a good performance in our system.

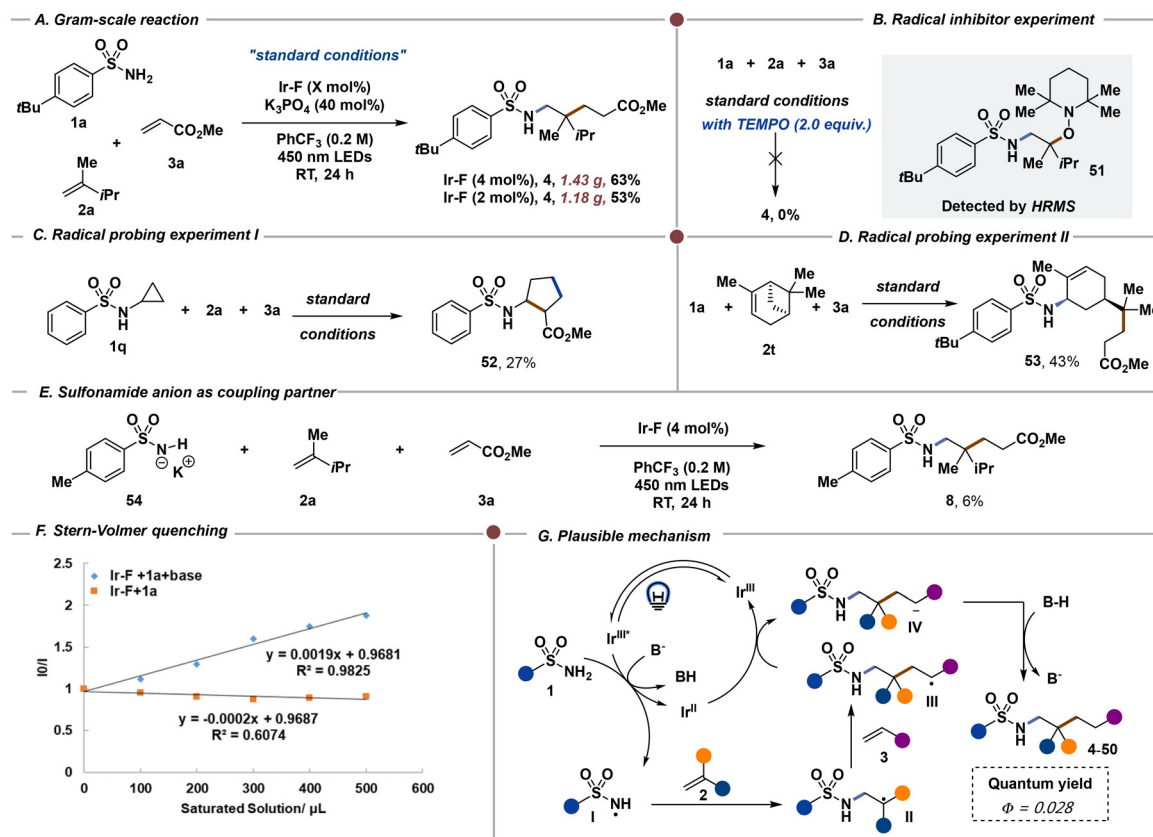
Gratifyingly, the standard reaction conditions tolerate a wide range of Michael acceptors containing different functional groups, such as alkyne (37), alkyl (38 and 43), nitrile (39), bromide (40), chloride (41), sulfoxide (42), and ketone (44), with moderate to high yields (Scheme 3). Furthermore, we also applied this atom-economical method in the late-stage modification of natural products. When 7-ketolithocholic methyl ester (45), carvone (46), cedrol (47), fenofibric acid (48), androsterone (49) and gemfibrozil (50) derived olefins were employed, the three-component products 45–50 could be

obtained in 42% to 81% isolated yields, respectively. Unfortunately, when an α,β -unsaturated Michael acceptor was employed as a coupling partner, the desired three-component coupling product could not be formed.

Mechanistic study

We also scaled up this three-component reaction, and the desired product 4 could be obtained with 63% isolated yield. When the photocatalyst was reduced to 2 mol%, the yield of 4 was still achievable at a 53% isolated yield (Scheme 4A). With two equivalents of TEMPO, the coupled product 4 could not be produced and the TEMPO-adduct 51 could be detected by HRMS (Scheme 4B). Meanwhile, when the sulfonamide 1q containing a three membered ring was employed under the standard conditions, the cyclized product 52 was obtained in 27% isolated yield, indicating that the nitrogen centered radical was formed which resulted in the ring opening and cyclization process (Scheme 4C).¹⁹ Additionally, the unactivated alkene 2t was also employed under the standard conditions, and the ring opening product 53 could be produced in 43% isolated yield, which also demonstrated that radical intermediates were involved in this three-component reaction (Scheme 4D). Using cyclic voltammetry, we found that 4-methylbenzenesulfonamide 1e undergoes oxidation at +2.21 V vs. SCE in MeCN. Therefore, direct electron transfer between this sulfonamide 1e and the excited state of Ir-F ($E_{1/2}^{\text{red}}[^* \text{Ir(III)}/\text{Ir(II)}] = +1.21$ V vs. SCE in MeCN)²⁰ is unlikely. Furthermore, the pK_{a} of benzenesulfonamide in MeCN is approximately 27,^{12a}





Scheme 4 Mechanistic studies and proposed mechanism.

making it unlikely to be deprotonated by K_3PO_4 . We also found that the oxidation of the corresponding potassium sulfonamide **54** occurs at approximately +1.28 V vs. SCE in MeCN using cyclic voltammetry, which did not match the oxidation potential of **Ir-F**. Furthermore, we performed the three-component reaction between **54**, **2a** and **3a** with 4 mol% **Ir-F** (Scheme 4E), and the desired coupling product **8** was obtained in only 6% yield. This result indicates that the oxidation of the sulfonamide anion to form nitrogen radical species is unlikely. Additionally, using Cs_2CO_3 , a weaker base ($pK_a = 10.3$) also provides the desired product **4** with similar yield (Table 1, entry 17). A Stern–Volmer quenching experiment was also performed and the excited photocatalyst **Ir-F** could only be quenched with a mixture of sulfonamide **1a** and base (Scheme 4F). Based on the current mechanistic results and recent hydroamination of alkenes by Knowles and co-workers,^{12a} we propose the following mechanism shown in Scheme 4G. The nitrogen-centered radical **I** is likely generated through the proton-coupled electron-transfer (PCET) pathway. After radical addition between **I** and unactivated alkene **2**, the newly formed radical intermediate **II** could further react with the electron-deficient alkene **3** to produce the radical intermediate **III** which could be further reduced to the anion intermediate **IV**. After the protonation step, the final coupled products **4–50** were produced efficiently. The quantum yield of this three-component reaction was measured ($\Phi = 0.028$)

which demonstrated that chain reaction is unlikely to have occurred under the current reaction conditions.

Conclusions

In summary, we have demonstrated a catalytic radical three-component reaction employing primary sulfonamides as nitrogen radical precursors. This mild and atom-economical method successfully coupled the primary sulfonamide, unactivated olefin and Michael acceptor with only a catalytic amount of photocatalyst and a simple inorganic base. This coupling reaction could tolerate a variety of functional groups and natural product modification. We hope that this newly developed method will be quickly adopted by the synthetic community and inspire further development regarding nitrogen centered radical triggered multicomponent reactions.

Data availability

The data supporting this article have been included as part of the ESI.† CCDC 2335224 (**4**) contains the supplementary crystallographic data for this paper.†



Conflicts of interest

There are no conflicts to declare.

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