RESEARCH ARTICLE

Visible-light-mediated allylation of alkyl radicals with allylic sulfones *via* a deaminative strategy†
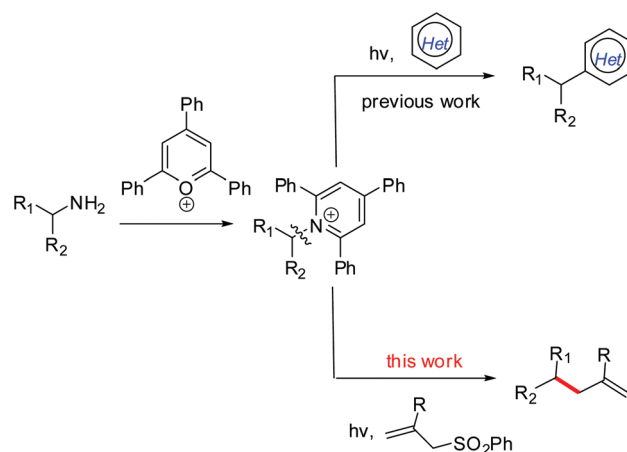
Miao-Miao Zhang[a] and Feng Liu ⓘ *[a,b]

A visible-light-mediated radical allylation of primary amine-derived Katritzky salts with allylic sulfones *via* C(sp³)–N bond activation is reported, furnishing the corresponding alkenes in satisfactory yields. This mild protocol provides an efficient strategy for site-specific C(sp³)–C(sp³) bond formation using abundant feedstock primary amines, particularly α-amino acids as alkyl radical precursors. This photocatalytic reaction demonstrates a broad substrate scope and good functional group tolerance.

Introduction

The development of synthetic methods for the generation of alkyl radicals from naturally abundant and cheap feedstock-derived radical precursors is of considerable interest for chemists.[1] Notably, a decarboxylative strategy using readily available carboxylic acids for radical alkylation,[2] especially with redox-active esters,[3,4] has received significant attention, as well as the use of amino acid-derived redox-active esters as precursors of α-aminoalkyl radicals.[5] Like carboxylic groups prevalent in molecules, the presence of amino (NH₂) groups in a variety of molecules, from simple building blocks to natural products and medicinally relevant compounds,[6] makes them a perfect synthetic handle for further transformations or late-stage modifications. However, the generation of alkyl radicals *via* C(sp³)–N bond activation still remains under-explored though the conversion of C(sp²)–NH₂ into radical precursors has been well established *via* the formation of diazonium salts.[7] Fortunately, bench-stable Katritzky pyridinium salts which are readily obtained from the condensation of primary amines with 2,4,6-triphenylpyrylium in one step[8] can act as alkyl radical precursors.[9] Of these few reports, Watson and co-workers described a nickel-catalyzed cross-coupling between redox-activated Katritzky salts and boronic acids *via* a C–N bond activation process.[9a,b] As a photoredox catalysis example, the Glorius group developed a visible-light-mediated protocol

for the deaminative generation of alkyl radicals *via* single-electron-transfer (SET) reduction of redox-active Katritzky salts ($E_{1/2} = -0.93$ V *vs.* SCE in DMF[10]), followed by a Minisci-type reaction to give alkylated heterocycles (Scheme 1).[9c] Despite these reports, the use of a deaminative strategy, especially the C(sp³)–N bond activation in the design and development of new radical reactions is still desirable.

As one of the C–C bond formation methods, radical allylation usually involves an addition of a carbon-centered radical to a suitable allylic reagent and then a fragmentation to rebuild a double bond.[11] So far, a series of alkyl radical precursors, such as alkyl halides,[12] boronates,[13] carboxylic acids,[14] redox-active esters,[15] and *N*-alkoxy-phthalimides,[16] have been used in the radical allylation reactions, in which allyl sulfones often served as efficient radical acceptors and allylation partners. To expand the utility of primary amine-derived Katritzky salts in radical reactions, we herein report a visible-light-

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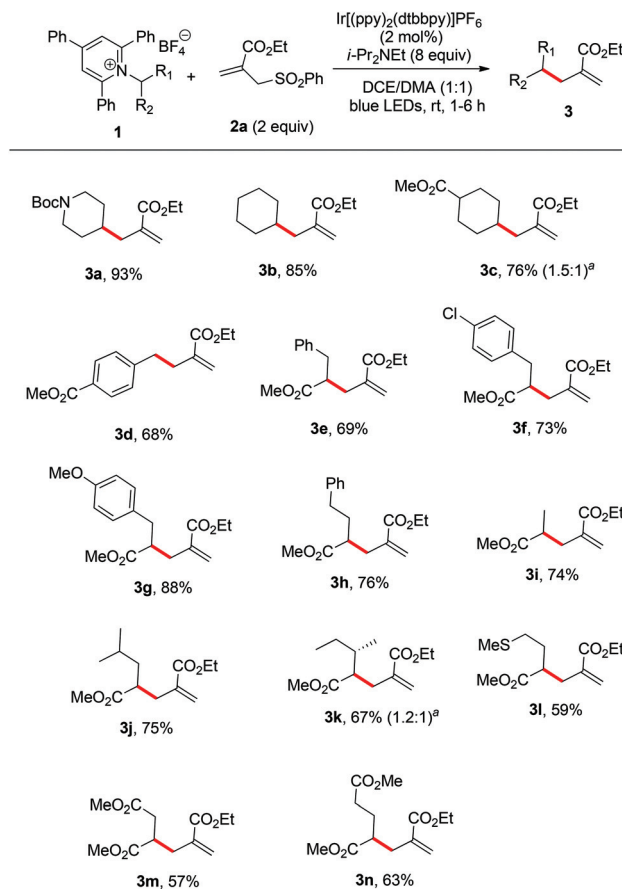
Scheme 1 Visible-light-mediated C–C bond formation *via* the deaminative strategy.

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mediated protocol for the allylation of alkyl radicals generated by a reductive deamination process, providing a general and efficient strategy for site-specific C–C bond formation (Scheme 1).

Results and discussion

Initially, an *N*-Boc-aminopiperidine-derived Katritzky salt (**1a**) and alkyl sulfone (**2a**) were chosen as the model substrates for the optimization of the reaction parameters (Table 1). The tertiary amine Hünig's base (i-Pr$_2$NEt, DIPEA) was used as the superstoichiometric reductant and Ir[(ppy)$_2$(dtbbpy)]PF$_6$ was employed as the photocatalyst. Upon irradiation with household blue LEDs (22 W) at ambient temperature for 3 h, we observed the formation of the desired alkene **3a** in 74% yield (entry 1). We next examined the influence of the amount of DIPEA and the results showed that 5 or 10 equiv. of the reductant turned out to be inferior (entries 2 and 3). Meanwhile, other reductant triethylamine (entry 4) and other commonly used photocatalysts Ir(ppy)$_3$ and Ru(bpy)$_2$Cl$_2$ (entries 5 and 6) were also tested, but they delivered product **3a** in lower yields. A brief screening of organic solvents (entries 7–16) showed that a co-solvent system DCE/DMA (1 : 1) was the best one in terms of chemical yield (entry 13). Control experiments demonstrated that the photocatalyst and visible light were both essential for the success of the reaction (entries 17 and 18).

With the optimized conditions in hand, we next evaluated the scope of primary amine-derived Katritzky salts in this

Table 1 Optimization of the reaction conditions[a]

Entry	Solvent	Photocatalyst	*t* (h)	Yield[b] (%)
1	MeCN	Ir[(ppy)$_2$(dtbbpy)]PF$_6$	3	74
2[c]	MeCN	Ir[(ppy)$_2$(dtbbpy)]PF$_6$	3	69
3[d]	MeCN	Ir[(ppy)$_2$(dtbbpy)]PF$_6$	5	66
4[e]	MeCN	Ir[(ppy)$_2$(dtbbpy)]PF$_6$	16	60
5	MeCN	Ir(ppy)$_3$	12	16
6	MeCN	Ru(bpy)$_2$Cl$_2$	3	69
7	DMA	Ir[(ppy)$_2$(dtbbpy)]PF$_6$	3	67
8	DMSO	Ir[(ppy)$_2$(dtbbpy)]PF$_6$	6	25
9	DCM	Ir[(ppy)$_2$(dtbbpy)]PF$_6$	3	71
10	DCE	Ir[(ppy)$_2$(dtbbpy)]PF$_6$	3	84
11	PhCl	Ir[(ppy)$_2$(dtbbpy)]PF$_6$	12	73
12	DCM/DMA (1 : 1)	Ir[(ppy)$_2$(dtbbpy)]PF$_6$	3	66
13	**DCE/DMA (1 : 1)**	**Ir[(ppy)$_2$(dtbbpy)]PF$_6$**	**3**	**93**
14	PhCl/DMA (1 : 1)	Ir[(ppy)$_2$(dtbbpy)]PF$_6$	3	81
15	DCE/DMA (2 : 1)	Ir[(ppy)$_2$(dtbbpy)]PF$_6$	3	87
16	DCE/DMA (1 : 2)	Ir[(ppy)$_2$(dtbbpy)]PF$_6$	3	89
17	DCE/DMA (1 : 1)	—	12	0
18[f]	DCE/DMA (1 : 1)	Ir[(ppy)$_2$(dtbbpy)]PF$_6$	12	0

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), photocatalyst (2 mol%), DIPEA (1.6 mmol), solvent (2 mL), room temperature, irradiation with household blue LEDs (22 W). [b] Isolated yield. [c] DIPEA (10 equiv.). [d] DIPEA (5 equiv.). [e] Et$_3$N (8 equiv.). [f] In the dark.

Scheme 2 Substrate scope of Katritzky salts. Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), Ir[(ppy)$_2$(dtbbpy)]PF$_6$ (2 mol%), DIPEA (1.6 mmol), DCE/DMA (1 : 1, 2 mL), room temperature, irradiation with blue LEDs (22 W), 1–6 h. [a] The dr value was determined by ^{1}H NMR.
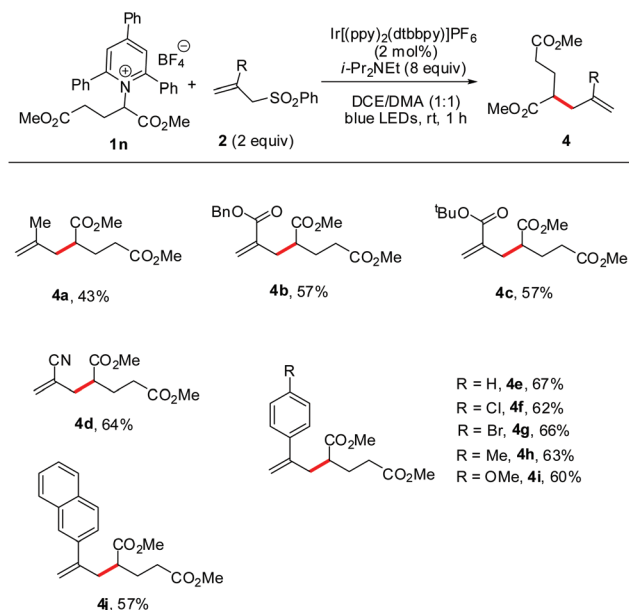
radical allylation reaction. As illustrated in Scheme 2, a variety of cyclic and acyclic alkyl radicals generated from Katritzky pyridinium salts were allylated in good to excellent yields (**3a–n**). Considering the fact that amino acids are naturally abundant feedstocks, the use of amino acids as radical precursors would be practical.[5] Although these conditions were optimized for common alkyl primary amine-derived Katritzky salts, they can also be applied to the amino acid-derived Katritzky salts (**3e–n**). The accommodated substrates derived from natural amino acids include phenylalanine (**3e**), tyrosine (**3g**), alanine (**3i**), leucine (**3j**), isoleucine (**3k**), methionine (**3l**), aspartic acid (**3m**), and glutamic acid (**3n**). The mild nature of this protocol allows it to tolerate a wide range of functional groups, including carbamate, ester, ether, and sulfide moieties. It should be mentioned that the reaction of a benzylic pyridinium salt could also proceed smoothly to give the desired product (**3d**). As most of the radical reactions, the diastereoselectivity of this reaction is also poor (**3c** and **3k**).

Furthermore, we turned our attention to defining the scope of allyl sulfones that are suitable for this radical reaction. As shown in Scheme 3, when using a glutamic acid-derived Katritzky salt (**1n**) as the radical precursor, a series of desired
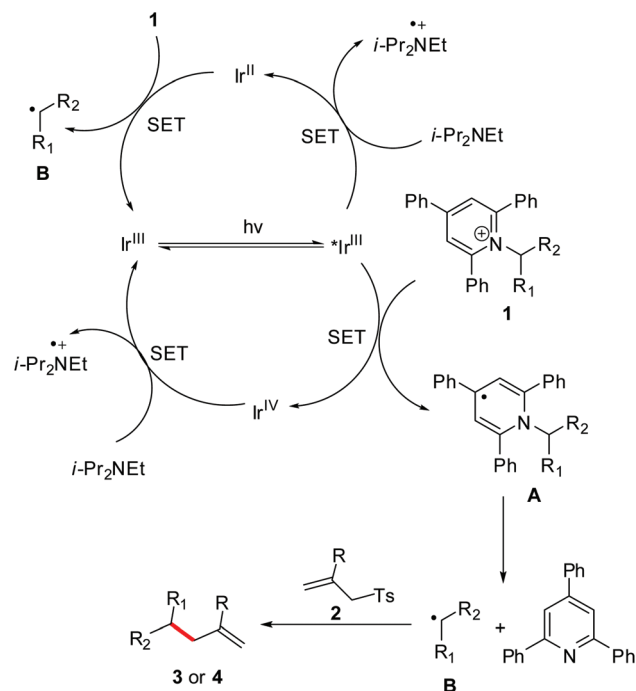
Scheme 3 Substrate scope of allyl sulfones. Reaction conditions: **1n** (0.2 mmol), **2** (0.4 mmol), Ir[(ppy)$_2$(dtbbpy)]PF$_6$ (2 mol%), DIPEA (1.6 mmol), DCE/DMA (1 : 1, 2 mL), room temperature, irradiation with blue LEDs (22 W), 1 h.

Scheme 4 Proposed mechanism.

allylated products were furnished with satisfactory efficiency (**4a–j**). The allyl sulfones bearing methyl, ester, cyano, or aryl groups were all tolerated well under the reaction conditions though the electron-rich 2-methyl allylsulfone afforded product **4a** in a lower yield compared to others. Notably, in the examples of **4f** and **4g**, the intact chloro and bromo atoms reserved the options for further cross-coupling. These results could substantially extend the scope of application of this radical allylation.

To gain insights into the mechanism of this visible-light-mediated reaction, fluorescence quenching experiments were performed (Fig. S2†).[17] As might be expected, the results showed that both primary amine-derived Katritzky salt **1a** and i-Pr$_2$NEt quenched the photoexcited Ir[(ppy)$_2$(dtbbpy)]PF$_6$ (*[Ir]$^{3+}$)[18] effectively but allyl sulfone **2a** did not. Moreover, the addition of a radical scavenger TEMPO ((2,2,6,6-tetramethyl-piperidin-1-yl)oxyl) led to the formation of **3a** only in 21% yield under the standard reaction conditions, with a TEMPO-trapped product being detected by MS analysis (Fig. S1†).[17] These results could support the generation of an alkyl radical intermediate via a single electron transfer (SET) process.

On the basis of the observations and previous reports,[9c,12–16] a possible mechanism is depicted in Scheme 4. Firstly, redox-active Katritzky salt **1** accepts an electron from *[Ir]$^{3+}$, yielding a dihydropyridine radical **A** and then a fragmentation driven by the reformation of an aromatic pyridine ring to give an alkyl radical **B**. Subsequently, the radical **B** adds to the C=C bond of allyl sulfone **2**, followed by a desulfonation to give the desired product **3** or **4**. Meanwhile, single-electron reduction of the [Ir]$^{4+}$ intermediate by i-Pr$_2$NEt

regenerates the ground-state [Ir]$^{3+}$ complex to close the photoredox cycle. On the other hand, i-Pr$_2$NEt that serves as a stoichiometric reductant can also transfer an electron to *[Ir]$^{3+}$ to afford [Ir]$^{2+}$ species. This [Ir]$^{2+}$ intermediate is highly reducing, enabling transfer of an electron to Katritzky salt **1**. This event produces the radical **B**, as well as completing the photocatalytic cycle.

Conclusions

In conclusion, we have developed a visible-light-mediated allylation reaction of Katritzky pyridinium salts with allyl sulfones via a deaminative strategy. With Ir[(ppy)$_2$(dtbbpy)]PF$_6$ as the photocatalyst and i-Pr$_2$NEt as the reductant, this mild approach provides ready access to site-specific C(sp^3)–C(sp^3) bond formation using abundant feedstock primary amines, particularly α-amino acids as alkyl radical precursors. The generality of this protocol has been illustrated and a series of functional groups are well tolerated.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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17 See the ESI.†

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