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C–H Functionalization

Visible-Light-Driven Photocatalytic Activation of Inert Sulfur Ylides for 3-Acyl Oxindole Synthesis

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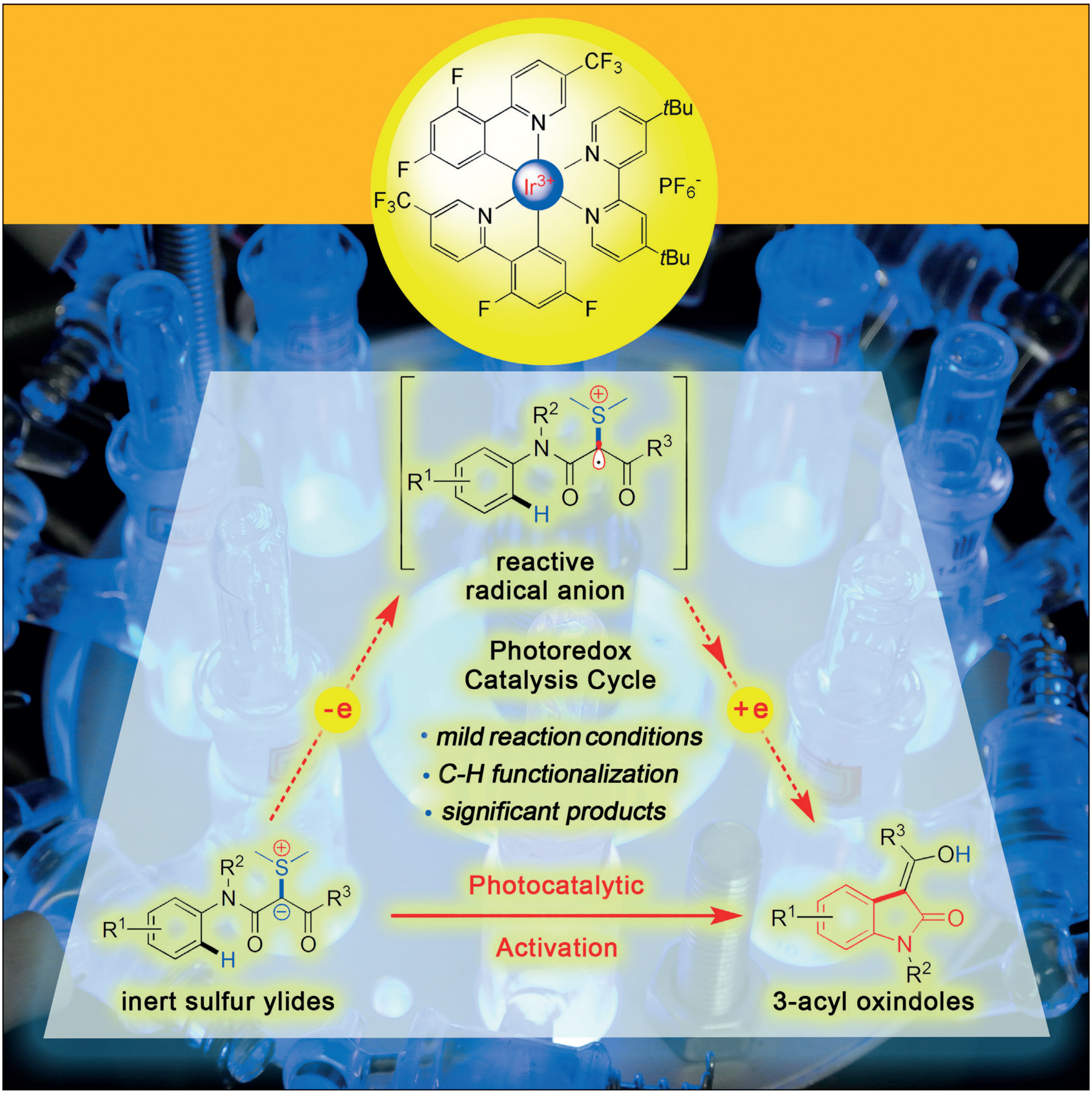
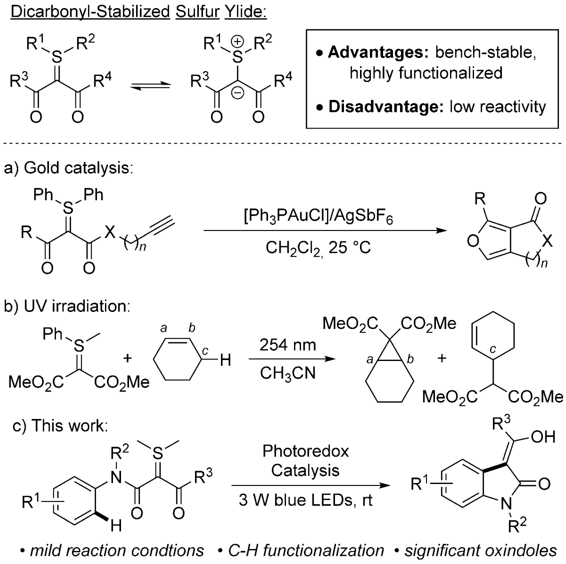


Abstract: Bicarbonyl-substituted sulfur ylide is a useful, but inert reagent in organic synthesis. Usually, harsh reaction conditions are required for its transformation. For the first time, it was demonstrated that a new, visible-light photoredox catalytic annulation of sulfur ylides under extremely mild conditions, permits the synthesis of oxindole derivatives in high selectivities and efficiencies. The key to its success is the photocatalytic single-electron-transfer (SET) oxidation of the inert amide and acyl-stabilized sulfur ylides to reactive radical cations, which easily proceeds with intramolecular C–H functionalization to give the final products.



Scheme 1. Reactivity of dicarbonyl-stabilized sulfur ylides.

Since the pioneering work in 1960s,[1] sulfur ylides have been a kind of privileged reagents in the field of carbocycle and heterocycle synthesis.[2] The unique reactivity of this broadly applied reagent is based on its carbanion structure, which is stabilized by an adjacent sulfonium ion. The additional delocalization of the carbanion by electron-withdrawing groups such as keto, ester, and amide groups makes this type of reagent more bench-stable, practical, and functionalized (Scheme 1). However, with these benefits, the sulfur ylides with double-electron-deficient functional groups usually exhibit low reactivity. Thus, notably few successful cyclizations of such sulfur ylides have been disclosed and harsh conditions (e.g., heating and Lewis acid catalysis) and highly electron-deficient alkenes are usually required.[3] In 2012, Maulide and co-workers reported an impressive annulation reaction of dicarbonyl-stabilized sulfur ylides and alkynes under mild conditions by subtly applying the strategy of gold catalysis to activate the sulfur ylide acceptors (Scheme 1a).[4a,5] Importantly, this strategy is general and can be widely applied to many other transformations of alkenes and allenes with stable sulfur ylides.[4b–e] In contrast to this strategy, we recently questioned whether such sulfur ylides themselves could be activated by a single-electron-transfer (SET) oxidation using visible-light photoredox catalysis, forming radical-cation-type electrophiles for annulation reactions.

The photochemical reactions of sulfur ylides remain underdeveloped because of their poor selectivity and because they typically require high-energy UV irradiation.[6] For example, Jenks' group in 2007 reported that diester-stabilized sulfur ylides could be photolysed at 254 nm to generate active carbene intermediates (Scheme 1 b).[6e] These active species easily react with excess cyclohexene to produce cyclopropanation or allylation products, with moderate chemoselectivities. Recently, visible-light-induced photocatalysis has been widely applied in organic synthesis to construct many kinds of heterocyclic compounds.[7] For example, Yu's group reported a very nice work on the synthesis of oxindoles by visible-light photoredox catalysis with the bromosubstituted analogue acting as the quenching reagent.[8] As part of our research program on heterocycle syntheses[9] using sulfur ylides and visible-light photocatalysis, we developed a new annulation reaction of amide and acyl-stabilized sulfur ylides for the first time (Scheme 1 c). This process provides an alternative route to biologically significant 3-acyl oxindole products[10] under extremely mild reaction conditions. Notably, the construction of oxindoles has been an important platform to develop new reaction methodologies, including visible-light photocatalysis strategy with diazo,[9g] and *N*-arylacrylamide compounds[11] as starting materials.

We first examined this visible-light-driven photochemical reaction with amide- and acetyl-stabilized sulfur ylide **1a** as the model substrate. The reaction was performed in THF at room temperature with [Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ (abbreviation: [Ir]; $E^{\propto}_{1/2} = +1.21$ versus saturated calomel electrode (SCE) in CH$_3$CN; dF(CF$_3$)ppy = 2-(2,4-difluorophenyl)-5-trifluoromethylpyridine; dtbbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine)[7f] as the photocatalyst (PC). The starting material **1a** was completely consumed after 7 h, and the enol-formed 3-acetyl oxindole product **2a** was obtained. Although the product contained some unconfirmed impurities, this problem was well resolved by adding 2.0 equivalents of KH$_2$PO$_4$,[12] and the pure product **2a** was obtained in 82% yield under a prolonged reaction time (Table 1, entry 1). The solvent effect was further investigated, but no better result was obtained in other reaction media. For example, ether solvents such as dioxane and diethyl

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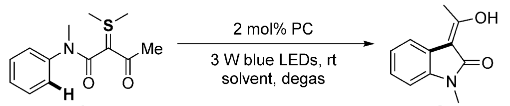
Table 1. Optimization of the photochemical annulation of **1a**.[a]



1a **2a**

Entry	Photocatalyst ($E_{1/2}^{ox}$)	Solvent	Result [%][b]
1	[Ir] (+1.21 V)	THF	82
2	[Ir] (+1.21 V)	dioxane	62
3	[Ir] (+1.21 V)	Et_2O	44
4	[Ir] (+1.21 V)	CH_2Cl_2	40
5	[Ir] (+1.21 V)	DMF	20
6	[Ir] (+1.21 V)	CH_3CN	24
7	[Ir] (+1.21 V)	*i*PrOH	15
8	[Ir] (+1.21 V)	EtOH	trace
9	Mes-Acr (+2.06 V)	THF	17
10	Eosin Y (+0.83 V)	THF	NR
11	$[Ru(bpy)_3(PF_6)_2]$ (+0.77 V)	THF	NR
12	*fac*-$[Ir(ppy)_3]$ (+0.31 V)	THF	NR
13[c]	[Ir] (+1.21 V)	THF	NR
14	–	THF	NR
15[d]	[Ir] (+1.21 V)	THF	0

[a] Conditions: sulfur ylide **1a** (0.3 mmol), KH_2PO_4 (2.0 equiv), PC (2 mol%), solvent (6.0 mL), Ar atmosphere, 3 W blue-LEDs irradiation, rt, 16 h. [b] Isolated yields. [c] Without visible light. [d] Air atmosphere. NR = No reaction. DMF = *N*,*N*-Dimethylformamide. bpy = 2,2′-Bipyridine. ppy = 2-phenylpyridine.

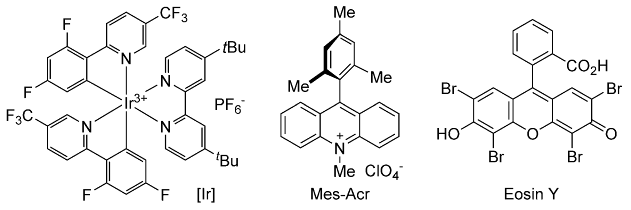
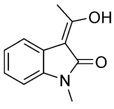
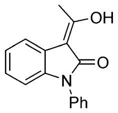


Table 2. Photochemical annulation: Sulfur ylide scope.[a]

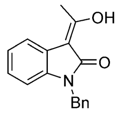
1 **2**



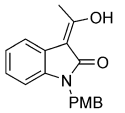
2a: 16 h, 82%



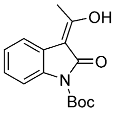
2b: 16 h, 64%



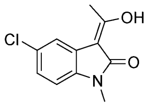
2c: 16 h, 64%



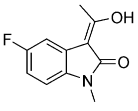
2d: 16 h, 62%



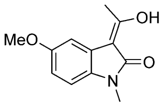
2e: 24 h, NR



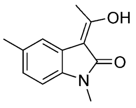
2f: 24 h, 69%



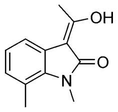
2g: 20 h, 80%



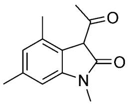
2h: 48 h, 52%



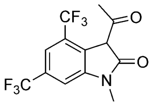
2i: 16 h, 68%



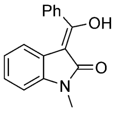
2j: 24 h, 77%



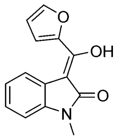
2k: 6 h, 92%



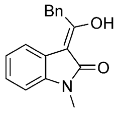
2l: 6 h, 46%



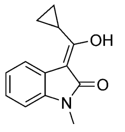
2m: 12 h, 57%



2n: 24 h, 56%



2o: 16 h, 72%



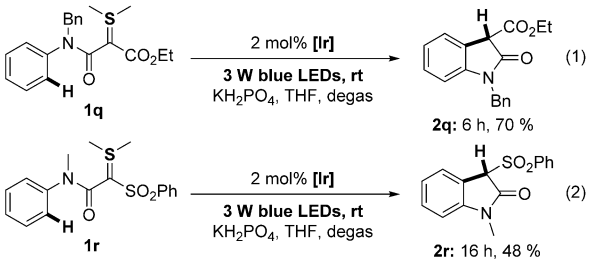
2p: 16 h, 67%

[a] Conditions: sulfur ylide **1** (0.3 mmol), KH_2PO_4 (2.0 equiv), [Ir] (2 mol%), THF (6.0 mL), Ar atmosphere, 3 W blue-LEDs irradiation, rt, indicated time; isolated yields. NR = No reaction. PMB = *p*-Methoxylbenzyl.

ether provided the product in 62 and 44% yield, respectively, at the level of full conversion (entries 2–3). Solvents such as CH_2Cl_2, DMF, and MeCN did not efficiently furnish the transformation and delivered the desired product **2a** in modest to moderate yields (entries 4–6). Alcohol solvents such as isopropanol and ethanol were also studied; however, only 15% yield or a trace amount of **2a** was detected, with most of the starting material intact (entries 7 and 8). We next evaluated numerous other photocatalysts for this transformation. For example, Mes-Acr, which has a high oxidative potential in its excited state[13] to catalyse the oxidative transformation of alkenes, sulfinates, 2*H*-azirines, and carboxylic acids, only accomplished this annulation reaction in a low yield (entry 9, 17% yield). Other photosensitizers such as organic dye Eosin Y[13] and metal complexes *fac*-$[Ir(ppy)_3]$ and $[Ru(bpy)_3(PF_6)_2]$[7f] did not respond to the optimized reaction conditions. Finally, the control experiments revealed that visible light and the photocatalyst were indispensable elements for the present annulation reaction of sulfur ylides (entries 13 and 14). When the photochemical annulation of **1a** was performed under an air atmosphere, this reaction system was complex and no desired product was observed (entry 15).

After having determined the optimal conditions, we evaluated the scope of sulfur ylides that could participate in this visible-light-induced photocatalytic annulation reaction. As outlined in Table 2, the tolerance of substituent groups on the nitrogen atom was first investigated. The results show that these mild reaction conditions tolerate a series of substituents, such as methyl, phenyl, benzyl, and *p*-methoxylbenzyl, and produce the corresponding oxindole products with large variations on the nitrogen atom (**2a**–**d**: 62–64%). The Boc-protected (Boc = *tert*-butoxycarbonyl) substrate (**1e**) did not react under optimized conditions. We then selected *N*-methyl amide-stabilized sulfur ylides to further study the electronic and steric effect on the benzene ring of aniline. Consequently, a wide range of substituted patterns on the aromatic ring was found to be compatible with these photoredox catalysis conditions. For example, all sulfur ylides with halogen atoms (e.g., Cl and F) and electron-donating groups (e.g., MeO and Me) on the benzene ring can be converted into the corresponding products in moderate to good yields (**2f**–**i**: 52–80% yields). When a methyl group was substituted on the *ortho*-position of the nitrogen atom, the 7-methyl oxindole derivative **2j** was isolated in 77% yield; when two substituents were introduced (e.g., Me and CF_3) at the *meta*-positions, ketone-formed oxindole derivatives **2k** and **2l** were obtained in 92 and 46% yield, respectively.

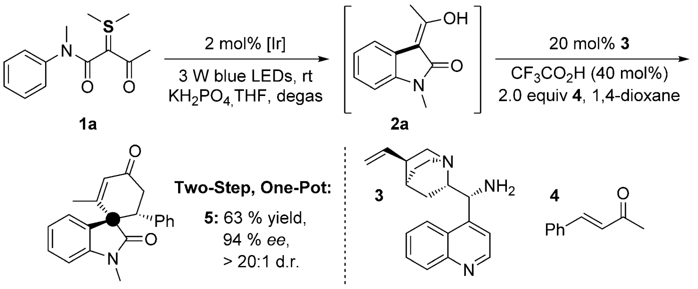
We further evaluated the diversity of the acyl group on sulfur ylides (R^3). For example, sulfur ylides with aryl- and heteroaryl-substituted acyls were also useful and were transformed into oxindole products in acceptable yields (**2m**: $R^3 =$ phenyl, 57% yield; **2n**: $R^3 =$ 2-furanyl, 56% yield). In the case of aliphatic substituents, this transformation can also convert the sulfur ylides into the desired products in satisfactory yields (e.g., **2o**: $R^3 =$ benzyl, 72% yield; **2p**: $R^3 =$ cyclopropyl, 67% yield). In addition to the acyl moieties on sulfur ylides, other electron-withdrawing groups were demonstrated to be successful for this visible-light-induced photochemical annulation. For example, when the sulfur ylides with an ester group (**1q**) or a benzenesulfonyl group (**1r**) were subjected to the standard conditions, 3-ester oxindole **2q** and 3-sulfonyl oxindole **2r** were produced in 70 and 48% yield, respectively [Eqs. (1) and (2)].



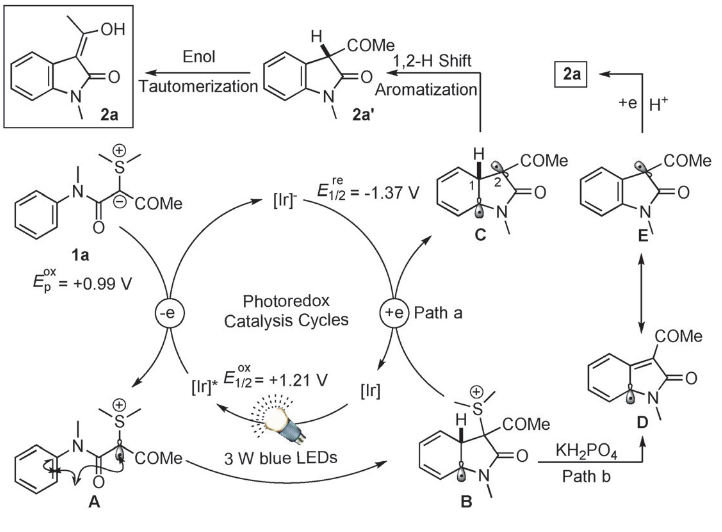
We then selected 3-acetyl oxindole **2a** as a versatile platform for further synthetic manipulations. For instance, as highlighted in Scheme 2, 20 mol% of chiral amine catalyst **3**, 40 mol% of trifluoroacetic acid, and 2.0 equivalents of benzalacetone **4** were added to the reaction mixture after full conversion of the starting material **1a** and replacement of the solvents. As a result, this two-step, one-pot operation rapidly produced the chiral spirocyclic oxindole **5** in good yield with excellent enantio- and diastereocontrol (63% yield, 94% *ee*, >20:1 d.r.).[14] This sequence of photocatalytic annulation and organocatalytic asymmetric Michael addition/aldol condensation undoubtedly demonstrates the synthetic utility of the present visible-light-driven photochemical reaction of sulfur ylides.

To better understand this photochemical annulation of sulfur ylides, we propose a possible reaction mechanism as illustrated in Scheme 3. The photocatalyst [Ir] is well known to readily absorb a photon under blue-LEDs irradiation to generate the excited photocatalyst [Ir]*, which has a strong oxidation potential.[7f] Sulfur ylide **1a**, which is a special carbanion, is assumed to be oxidized by the excited state of the photocatalyst [Ir]* to form the sulfonium-ion-connected radical species **A** (SET oxidation), which can be stabilized by the adjacent amide and acetyl groups. Presumably, species **A** is highly electrophonic and readily undergoes an intramolecular radical addition to the benzene ring to forge a new chemical bond, which concomitantly generates the radical intermediate **B**. After the generation of intermediate **B**, two possible pathways are proposed. In path a, an SET reduction of **B** by the strong reducing reagent $[Ir]^-$ delivers a transient radical intermediate **C** and simultaneously closes the photoredox catalytic cycle.[15] Intermediate **C** is then converted into ketone-formed 3-acetyl oxindole **2a′** through a 1,2-hydrogen shift/aromatization process. Finally **2a′** spontaneously transforms into the more stable, enol-formed product **2a** through a tautomerization process. In path b, KH_2PO_4 promotes the elimination process to furnish the intermediate **D** with its resonance form **E**. They could then be reduced by the photocatalyst and reprotonated to give the final compound **2a**.

To support this proposed redox-neutral photocatalytic process, we first characterized substrate **1a** in CH_3CN using CV, which revealed the oxidation potential of **1a** to be $+0.99$ V versus SCE.[16] Hence, the SET oxidation of sulfur ylide **1a** by the excited state of [Ir]* ($+1.21$ V vs. SCE) should be thermodynamically favourable. We then carried out the fluorescence quenching experiment with **1a**, and substrate **1a** can unambiguously quench the excited [Ir]*.[16] Moreover, the quantum yields (Φ) of the process were measured at four stages of conversion,[17] which were 2, 4, 6, and 8 min, respectively and the corresponding quantum yields were 28, 29, 28, and 30%.[16] Quantum yields of these magnitudes ($\Phi < 1$) support the feasibility of the proposed mechanism, although it cannot com-



Scheme 2. Synthetic manipulation: asymmetric synthesis of chiral spirocyclic oxindole **5**.



Scheme 3. Possible reaction mechanism.

pletely rule out the chain propagation process. In addition, the reaction was completely shut down by the addition of 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO), which suggests that radicals were involved in this photochemical annulation reaction of sulfur ylides. On the other hand, in order to rule out the generation of the carbene intermediate through an energy-transfer pathway,[9g] we added 2.0 equivalents of 1,4-diazobicyclo[2.2.2]octane (DABCO), an electron-donating quencher of the photocatalyst,[6d] to the model reaction under the standard conditions. As a result, no reaction occurred after 16 h with sulfur ylide **1a** remaining. In addition, according to Schuster's work,[6d] carbene intermediate was easily reacted by an O–H insertion reaction in the presence of excess alcohols. However, except for the observation of a small amount of the product **2a**, a large amount of the starting material **1a** is still intact in the alcohol solvents (Table 1, entries 7–8). Therefore, we believed that the carbene intermediate was less likely involved in this reaction based on the current experimental evidence.

In conclusion, we have developed a new, visible-light photoredox catalytic annulation reaction of sulfur ylides. This photochemical process enables the synthesis of oxindole derivatives in high selectivity and efficiency under extremely mild reaction conditions. Its success relies on the activation of inert dicarbonyl-stabilized sulfur ylides by photocatalytic SET oxidation, which generates reactive radical species that easily induce the intramolecular C–H functionalizations. We believe that the strategy of visible-light photoredox catalysis will pave the way to exploit a new annulation chemistry of sulfur ylides.

Experimental Section

General

To a 10 mL Schlenk tube equipped with a magnetic stirrer bar was added **1** (0.3 mmol, 1.0 equiv), KH_2PO_4 (0.6 mmol, 2.0 equiv), [Ir] (2 mol %), and THF (6 mL). The resulting mixture was degassed through a 'freeze-pump-thaw' procedure three times, and then the solution was stirred at room temperature under irradiation of 3 W blue LEDs. Upon the completion of the cycloaddition, as monitored by TLC analysis, the isolated yield was determined by flash chromatography on silica gel (petroleum ether/EtOAc = 4:1).

Acknowledgements

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Keywords: C–H functionalization · oxindoles · photocatalysis · sulfur ylides · visible light

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