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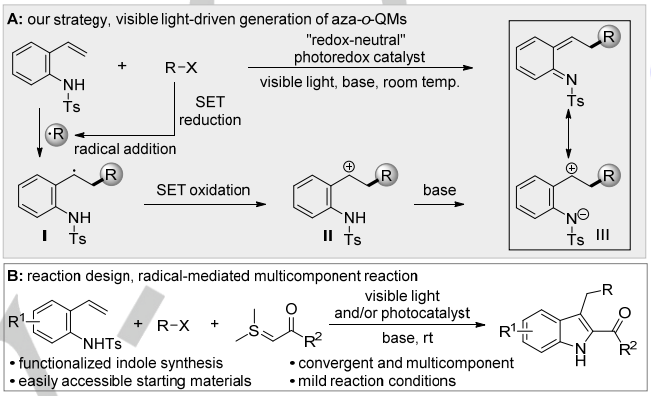
Visible Light-Driven Aza-*ortho*-Quinone Methide Generation Enables a Multicomponent Reaction

Yi-Yin Liu, Xiao-Ye Yu, Jia-Rong Chen,* Ming-Ming Qiao, Xiaotian Qi, De-Qing Shi, and Wen-Jing Xiao*

Abstract: *A visible light-driven radical-mediated strategy for the in situ generation of aza-ortho-quinone methides from alkenylanilines and alkyl radical precursors has been accomplished. This protocol enables an efficient multicomponent reaction of alkenylanilines, halides and sulfur ylides, and shows wide substrate scope and functional group tolerance. Treatment of the cycloaddition products with a base leads to a convenient synthesis of densely functionalized indoles in a single flask operation.*

Aza-*ortho*-quinone methides (aza-*o*-QMs) are highly reactive intermediates of value in many areas of chemistry and biology.[1] Owing to their sizeable propensity for rearomatization, aza-*o*-QMs can undergo various cycloaddition or nucleophilic addition to provide facile access to condensed heterocycles, 2-aminobenzyl derivatives and complex natural products.[2] In contrast to the chemistry of *o*-QMs that can be formed from a range of precursors,[3] however, the chemistry of aza-*o*-QMs has yet to be fully investigated due to a dearth of general methods for their convenient generation.

Traditional methods for the in situ formation of aza-*o*-QMs mainly rely on pyrolysis,[4] UV photolysis,[5] base[6] and Brønsted acid[7] promoted 1,4-elimination or tautomerization. In practice, pyrolysis and UV photochemical generation is rarely exploited in organic synthesis due to the requirement of unstable precursors, or their limited substrate scope and functional-group tolerance. Brønsted base and acid-mediated 1,4-elimination of *o*-chloromethyl anilines[8] and *o*-amino benzhydryl alcohols[9] have recently attracted a resurgence of interest in organic synthesis as one of the most powerful and benign methods for aza-*o*-QM generation. An appropriate combination of these methods with chiral organocatalysts can afford a suite of innovative and enantioselective transformations. However, in some cases, these pH-dependent protocols are complicated by pre-incorporation of leaving groups, lengthy substrate syntheses or limited generality. Tunge discovered an elegant Pd-catalyzed decarboxylative procedure to generate Pd-polarized aza-*o*-QMs from vinyl benzoxazinones under mild conditions.[10] These intermediates could undergo a variety of [4+n] cycloaddition (n = 1-4) reactions.[11] Recently, several Fe-, Cu-, and Ir-catalyzed metal-stabilized zwitterionic forms of aza-*o*-QMs have also been developed by Xiao, Lu, Gong and Yang.[12] In these processes, the terminal vinyl or ethynyl moieties are indispensable. While these methods greatly expanded the access to aza-*o*-QMs, the development of mechanistically distinct approaches for their generation, especially with concomitant installation of different functional groups is still desirable.



Scheme 1. Visible light-driven aza-*o*-QM generation and reaction design.

Recently, visible light photochemistry has been established as a powerful tool for the generation of various radicals and radical ions under mild conditions.[13] These radical intermediates enable facile incorporation of diverse valuable functionalities into alkenes.[14] In most of these processes, β-functionalized carbocations are typically engaged as the key intermediates after a single-electron transfer (SET) event. Recognizing the importance of this reactivity mode and the neutral and zwitterionic characteristics of aza-*o*-QMs, we questioned whether it is possible to explore the visible light-driven radical-mediated strategy for the in situ generation of aza-*o*-QMs from easily accessible alkenylanilines (Scheme 1A). Specifically, we surmised that visible light-driven photochemistry would transform the radical sources, such as simple halides, into electrophilic radicals via a SET process, which can then add to the alkene of alkenylanilines. Another SET oxidation of the radical intermediate **I** should lead to the β-substituted carbocation intermediate **II**. Finally, the intermediate **II** may be deprotonated by base to give the zwitterionic species **III**, which should be in resonance with its neutral aza-*o*-QM. If successful, this net redox neutral strategy would provide a complementary access to aza-*o*-QMs. However, this protocol might be complicated by potential side reactions, such as deprotonation of β-H of the carbocation **II** or its trap by nucleophilic solvent.[14] Here we disclose how this ideal was translated into experimental reality, enabling a multicomponent reaction for indole synthesis (Scheme 1B).[15,16]

We initially chose readily accessible *N*-Ts-2-alkenylaniline **1a** as a model substrate and Umemoto and Togni reagents as the CF_3 radical sources because of the unique physiological activity of this functional group,[17] to generate the corresponding aza-*o*-QMs based on our design plan.[18,19] Stable sulfur ylide **3a**

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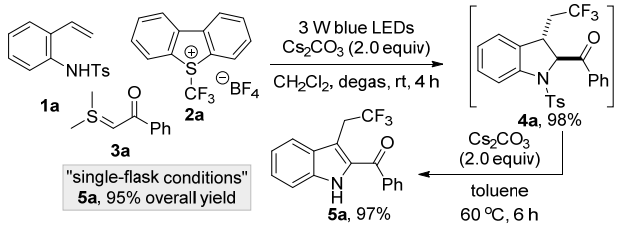
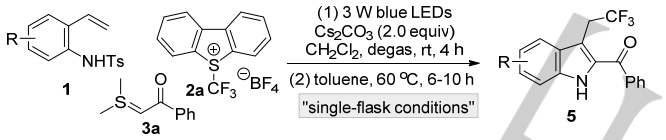
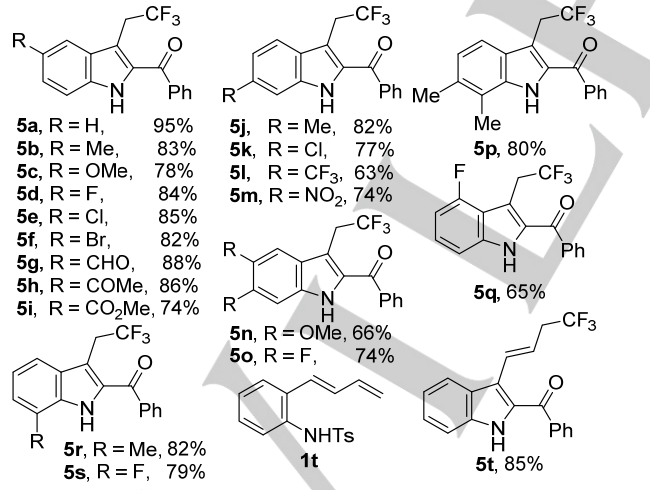
was exploited to intercept the in situ formed aza-*o*-QM via a formal [4+1] cycloaddition (Scheme 2).[20] Extensive optimization studies established that a combination of CH_2Cl_2 and Cs_2CO_3 resulted in a clean reaction under irradiation of 3 W blue LEDs in the absence of a photocatalyst, giving **4a** in 98% yield as a single diastereomer (See Tables S1-2 for more details).[21,22] This result implied that a photoactive electron donor-acceptor (EDA) aggregation of **1a** and **2a** might be involved in CF_3 radical generation.[23] Then, we attempted desulfonylation/aromatization of **4a** to synthesize indole **5a**. Gratifyingly, exposure of indoline **4a** to Cs_2CO_3 in toluene at 60 °C furnished the *N*-free indole **5a** in 97% yield. Notably, the synthesis of indole **5a** could be achieved in a single flask operation by replacing the volatile CH_2Cl_2 with toluene and increasing the reaction temperature to 60 °C upon consumption of **1a**, giving a 95% overall yield of **5a**.[22]



Scheme 2. Visible light-driven multicomponent reaction of alkenylanilines, halides and sulfur ylides for indole synthesis.

Table 1: Scope of the *N*-Ts-2-alkenylanilines.[a,b]



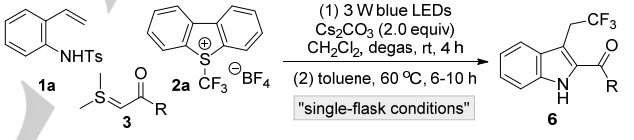


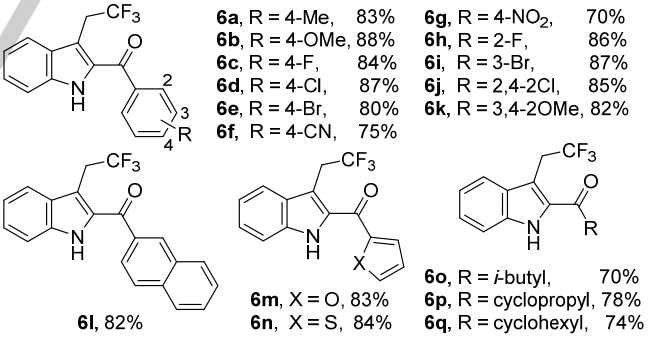
[a] **1** (0.2 mmol), **2a** (0.22 mmol), **3a** (0.30 mmol), Cs_2CO_3 (0.40 mmol), and CH_2Cl_2 (4.0 mL) at rt for 4 h under irradiation of 3 W blue LEDs. Upon consumption of **1**, CH_2Cl_2 was replaced with toluene and the mixture was warmed to 60 °C for 6-10 h. [b] Isolated yields.

First, we attempted to evaluate the substrate scope of *N*-Ts-2-alkenylanilines **1** (Table 1). The *N*-Ts-2-alkenylanilines **1a-f** bearing an electron-neutral, electron-donating (e.g., -Me, -OMe) or electron-withdrawing (e.g., -F, Cl, Br) substituent at the *para*-position were well tolerated, giving the products **5a-f** in 78-95% yields. Moreover, the reactions of substrates **1g-i** with a range of synthetically useful handles, such as aldehyde, ketone, and ester moieties proceeded well to furnish products **5g-i** in 74-88% yields. As also demonstrated in the synthesis of indoles **5j-q** (63-82% yield), the steric property or substitution pattern of the *N*-Ts-2-alkenylanilines has no obvious effect on the reaction efficiency. Notably, our protocol proved to be suitable for the synthesis of sterically encumbered C-7-substituted indoles **5r** and **5s**, which are inaccessible by previous methods.[8a,b] As for the substrate **1t** with a (*E*)-buta-1,3-dien-1-yl group at the *ortho*-position, the photo-generated CF_3 radical added to the alkene terminus to produce indole **5t** in 85% yield.

Encouraged by these results, we continued to examine the substrate generality of sulfur ylides **3** with **1a** and **2a** under the standard conditions. As highlighted in Table 2, the substitution patterns and electronic characteristics of the phenyl ring within sulfur ylides show no apparent effect on the reaction. A series of mono-substituted sulfur ylides bearing electron- donating and electron-withdrawing groups at the *para*-, *meta*- and *ortho*-positions of the aromatic ring all reacted nicely, affording the indole products **6a-i** in yields ranging from 70% to 88%. Furthermore, the disubstituted sulfur ylides **3j-k** were viable substrates for this reaction, with products **6j** and **6k** being formed in 85% and 82% yields, respectively. Heterocyclic thiophene- and furan-substituted sulfur ylides **3m** and **3n** readily participated in the reaction to afford products **6m-n** in high yields. The current catalytic system could also be extended to alkyacyl-substituted sulfur ylides, such as **3o-q**, giving the desired products **6o-q** in 70-78% yields.

Table 2: Scope of the sulfur ylides. [a,b]





[a] The conditions are the same as in Table 1. [b] Isolated yields.

Next, we proceeded to examine the substrate scope of halides as fluoro-containing radical sources using substrates **1a** and **3a** (Table 3). However, the above-mentioned photocatalyst-free conditions proved to be ineffective likely due to the significantly diminished efficiency in the radical generation. Control experiments also showed that though colourless EDA complex was formed between **1a** and **7a**, such type of EDA complex is unable to generate fluoroalkyl radicals to initiate the expected reaction.[21] With heptafluoro-1-iodopropane **7a** as a radical source, a new cycle of optimization identified that employing photocatalyst $Ru(phen)_3Cl_2$ (phen = phenanthroline) along with NaOH as the base in CH_3CN was critical for the reactivity, thus enabling in situ generation of the corresponding

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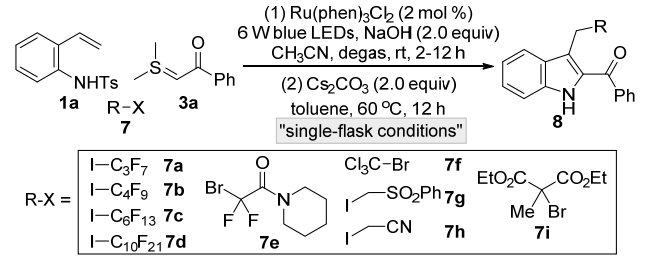
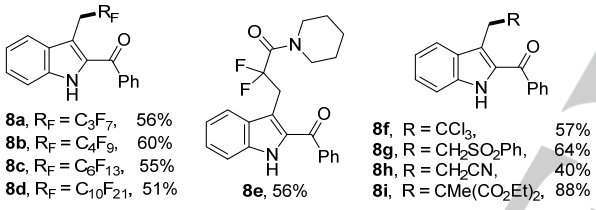
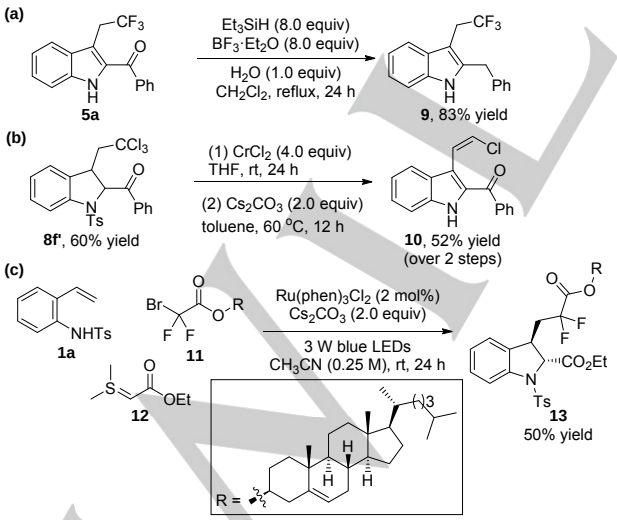
aza-*o*-QMs and its subsequent cycloaddition with the sulfur ylide **3a**.[21] At the completion of the cycloaddition step, CH_3CN was removed from the mixture by vacuum. Upon addition of Cs_2CO_3 and toluene, the initially formed indoline intermediate was transformed into to the corresponding indole **8a** in 56% overall yield. With the efficient single-flask conditions in hand, we examined the substrate scope of radical sources by using a range of perfluoroalkyl iodides **7b-d**. It was found that a longer perfluorinated chain could be efficiently installed at the alkene moiety, giving the indole products **8b-d** in good yields (51-60%). The reaction with 2-bromo-2,2-difluoroacet-amide **7e** as difluorinating reagent also worked well to afford **8e** in 56% yield. We then evaluated other compounds bearing activated C-X bonds. All the reactions of haloalkanes and α-halocarbonyls **7f-i** worked well to furnish the desired indoles **8f-i** in 40-88% yields.

Table 3: Scope of radical sources.[a,b]





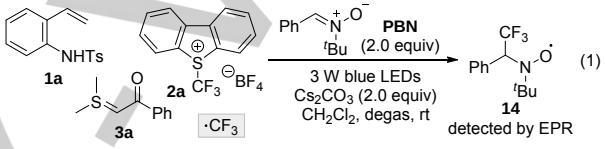
[a] **1a** (0.2 mmol), **7** (0.40 mmol), **3a** (0.30 mmol), NaOH (0.40 mmol), and CH_3CN (4.0 mL) at rt for 2-12 h under irradiation of 6 W blue LEDs. Upon consumption of **1a**, CH_3CN was replaced with toluene and Cs_2CO_3 (0.40 mmol) was added. The mixture was warmed to 60 °C for a further 12 h. [b] Isolated yields.



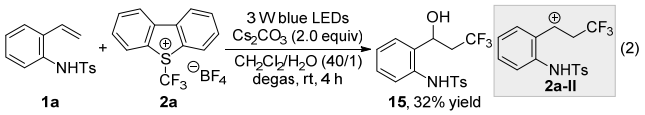
Scheme 3. Synthetic applications.

Then, we selected several transformations to highlight the synthetic potential of this methodology (Scheme 3). The carbonyl group in product **5a** could be easily converted to the methylene moiety, with the indole derivative **9** obtained in 83% yield (Scheme 3a). When the synthesis of indoline **8f'** was carried out in degassed CH_3CN under a continuous flow of argon under sunlight irradiation, the reaction efficiency could be significantly improved with comparable results. Indoline **8f'** could be conveniently further converted to 3-vinyl-substituted indole **10** in 52% overall yield (Scheme 3b).[21] The reaction of **1a**, cholesterol-derived bromide **11** and sulfur ylide **12** also proceeded smoothly to give a single stereoisomeric product **13** bearing a biologically important indoline scaffold in 50% yield (Scheme 3c).[22]

To gain some insights into the mechanism, we conducted a series of control experiments with model substrates **1a**, **2a** and sulfur ylide **3a**. In the presence of stoichiometric radical quencher TEMPO, significant inhibition of the reactivity was observed, suggesting that the process involves radical steps (Scheme S1).[21] Moreover, we monitored the model reaction by electron paramagnetic resonance (EPR) spectroscopy with the addition of *tert*-butyl-α-phenylnitrone (PBN) as a radical trap [Eq. (1)].[21] We detected signals that are clearly identified as EPR signals of the CF_3-PBN adduct according to the literature data (Figure S1).[24]



Moreover, we noticed that, after mixing with the base Cs_2CO_3, the achromatic solution mixture of **1a** and Umemoto reagent **2a** in CH_2Cl_2 spontaneously developed a yellow colour (Figure S2A); the optical absorption spectrum of the mixture also showed a bathochromic shift to the visible spectral region, indicative of an EDA complex (Figure S2B). These findings confirm the formation of a CF_3 radical through visible light-driven SET reduction of the Umemoto reagent **2a** and EDA complex activation.[23,24] Instead, in the case of other radical sources as described in Table 4, the control experiments suggested that a photocatalyst-promoted SET process was involved in the generation of the corresponding alkyl radicals though colourless EDA complex was also formed (Figure S3).[21] When the reaction of **1a** and **2a** was performed in a mixed solvent system of CH_2Cl_2 and H_2O (40:1) without sulfur ylide **3a**, we isolated hydroxytrifluoromethylation product **15** in 32% yield [Eq. (2)]. This result suggests that the β-CF_3-substituted carbocationic intermediate **2a-II** should be involved in the reaction.[14]



Finally, we propose a plausible mechanism for this reaction (Figure 1). The reaction is initiated by the visible light-induced SET reduction of Umemoto reagent **2a** and halides **7** through photochemically active EDA complex of type **I** or by the excited state $*[Ru(phen)_3]^{2+}$ (Figure 1a and 1b), giving the corresponding CF_3 and alkyl radicals. Interestingly, in the control experiment performed in the dark, a moderate yield of **4a** was obtained after 48 h, suggesting that such type of EDA could facilitate generation of CF_3 radical thermally to some extent though with low efficiency (Table S2).[21] An elegant work of Yu firstly demonstrated that an EDA complex of Umemoto reagent and an amine enabled generation of CF_3 radical and direct C-H trifluoromethylation of (hetero)arenes.[23h] Then, addition of these electrophilic radicals to the alkene moiety of **1a** provides radical intermediates **2a-I**

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and **7-I**, which are oxidized by another molecular of Umemoto reagent **2a** through radical chain propagation or by the oxidizing $[Ru(phen)_3]^{3+}$ species to form β-substituted carbocations **2a-II** and **7-II** with regeneration of ground-state $[Ru(phen)_3]^{2+}$, completing the photocatalytic cycle. Despite its low concentration,[21] an alternative mechanism involving direct addition of CF_3 and alkyl radicals to the deprotonated form **1a'** cannot be ruled out (Figure S5).[21] We determined the quantum yields of the reaction of **1a**, **2a**, and **3a**, and the reaction of **1a**, **2a**, and **7a** to be 7.2 and 1.03, respectively, which confirmed the proposed mechanistic bifurcation. Then, the intermediates **2a-II** and **7-II** undergo a facile deprotonation in the presence of the base to give aza-*o*-QMs **2a-III** and **7-III**. Calculation studies of carbocation **2a-II** demonstrated that the Cs_2CO_3-promoted formation of the aza-*o*-QM **2a-III** is exergonic by 55.3 kcal/mol (Figure S6).[21] A final formal [4+1] cycloaddition of the aza-*o*-QMs and sulfur ylide **3a** occurred to give the corresponding indolines, which were converted to the indoles **5a** and **8** by Cs_2CO_3-mediated E1cb elimination and aromatization.

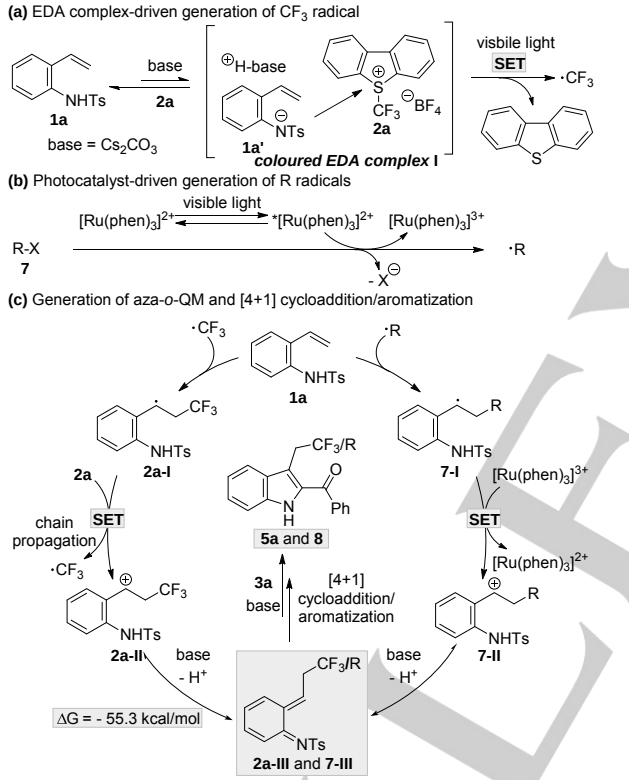

Figure 1. Possible reaction mechanism.

In summary, we have developed a visible light-driven radical-mediated strategy for the in situ generation of aza-*o*-QMs from readily accessible starting materials. This redox-neutral protocol enables an efficient multicomponent reaction of alkenylanilines, halides and sulfur ylides, leading to synthesis of diversely functionalized indole heterocycles in a single flask operation.

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Keywords: photochemistry • radicals • aza-ortho-quinone methides • sulfur ylides • indoles

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[21] See the Supporting Information for more details.

[22] CCDC 1546173 (**4a**), 1542636 (**5a**) and 1546967 (**13**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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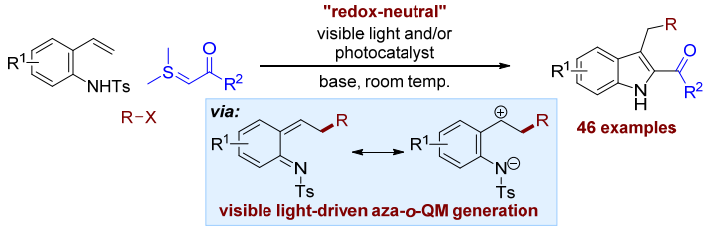

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Visible Light-Driven Aza-ortho-Quinone Methide Generation Enables A Multicomponent Reaction

A visible light-driven radical-mediated strategy for the in situ generation of aza-ortho-quinone methides from alkenylanilines and alkyl radical precursors has been accomplished. This protocol enables an efficient multicomponent reaction of alkenylanilines, halides and sulfur ylides, and shows wide substrate scope and functional group tolerance. Treatment of the cycloaddition products with a base leads to a convenient synthesis of densely functionalized indoles in a single flask operation.

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