Photoredox Catalysis

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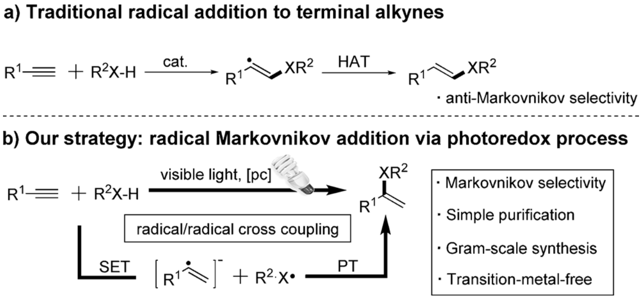
Markovnikov-Selective Radical Addition of S-Nucleophiles to Terminal Alkynes through a Photoredox Process

*Huamin Wang, Qingquan Lu, Chien-Wei Chiang, Yi Luo, Jiufu Zhou, Guangyu Wang, and Aiwen Lei**

Abstract: *Direct radical additions to terminal alkynes have been widely employed in organic synthesis, providing credible access to the anti-Markovnikov products. Because of the Kharasch effect, regioselective control for the formation of Markovnikov products still remains a great challenge. Herein, we develop a transition-metal-free, visible light-mediated radical addition of S-nucleophiles to terminal alkynes, furnishing a wide array of α-substituted vinyl sulfones with exclusive Markovnikov regioselectivity. Mechanistic investigations demonstrated that radical/radical cross-coupling might be the key step in this transformation. This radical Markovnikov addition protocol also provides an opportunity to facilitate the synthesis of other valuable α-substituted vinyl compounds.*



Scheme 1. Radical addition of H-heteroatom compounds to terminal alkynes. SET = single-electron transfer, PT = proton transfer, [pc] = photoredox catalyst.

Radical additions to terminal alkynes have long served as a powerful strategy to access complex molecules.[1] In this context, anti-Markovnikov products were obtained exclusively due to the Kharasch effect.[1,2] Consequently, strategies allowing for direct efficient synthesis of α-substituted vinyl compounds from intermolecular radical addition to terminal alkynes have rarely been reported.[2g] In principle, the stability of a radical intermediate generated from the radical addition step is the key for the final selectivity control, and anti-Markovnikov addition often gives the more stable radical intermediate (Scheme 1 a). Therefore, seeking a new channel to synthesize valuable α-substituted vinyl compounds through radical Markovnikov addition procedure is appealing and extremely challenging. Inspired by the state of the art of radical/radical cross coupling,[3] we wondered whether the Markovnikov products, α-substituted vinyl compounds, can be obtained through the general and useful cross-coupling of α-vinyl carbon radical and other organic radicals (Scheme 1 b).

According to the aforementioned concept, α-substituted vinyl sulfones, which not only serve as useful synthetic intermediates but also are widely featured in biologically active compounds,[4] were chosen as synthetic target molecules. The development of synthetic approaches to vinyl sulfones has received substantial attention in recent years.[5] Up to now, the majority of methods for the synthesis of vinyl sulfones lead to *trans*-configured β-substituted products.[5,6] Nevertheless, the synthesis of α-substituted vinyl sulfones, which have great potential application in biological sciences,[7] still remains an outstanding challenge. Established approaches to the synthesis of α-substituted vinyl sulfones usually contain several steps or rely on noble transition metal catalysts, suffering from poor regioselectivity and difficult purification.[7,8] An alternative strategy with more simple and sustainable perspective is therefore highly appealing.

Recently, visible light-mediated photoredox catalysis has emerged as a powerful tool in radical reactions.[3h–j,9] Thus, we envisioned that visible light-mediated photoredox catalysis might enable access α-substituted vinyl sulfones through radical processes. Herein, we describe a transition-metal-free, visible light-mediated Markovnikov addition of sulfinic acids to terminal alkynes via α-vinyl radical/sulfonyl radical cross-coupling. A wide array of α-substituted vinyl sulfones can be obtained with exclusive Markovnikov regioselectivity, some of which are difficult to generate by existing approaches.

To test the above hypothesis, phenylacetylene (**1a**) and *p*-toluenesulfinic acid (**2a**) were chosen as substrates (Supporting Information, Table S1). Firstly, eosin Y, widely used as a photoredox catalyst due to its low cost and simple purification,[10] was tested. To our delight, when the reaction of **1a** and **2a** was performed, the desired product **3a** was obtained in 19 % yield (Table S1, entry 1). Encouraged by the result, various bases, reacting with sulfinic acids to form sulfinate salts, were next investigated. Intriguingly, when the reaction was performed with K_2CO_3 as base, the Markovnikov product was exclusively obtained in 86 % yield (Table S1, entry 5). Further experiments have shown that the solvent has

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[*] H. Wang, Dr. Q. Lu, C. Chiang, Y. Luo, J. Zhou, G. Wang, Prof. A. Lei
The Institute for Advanced Studies (IAS), College of Chemistry and Molecular Sciences, Wuhan University
Wuhan 430072, Hubei (P.R. China)
E-mail: aiwenlei@whu.edu.cn

Prof. A. Lei
Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou 730000 (P.R. China)

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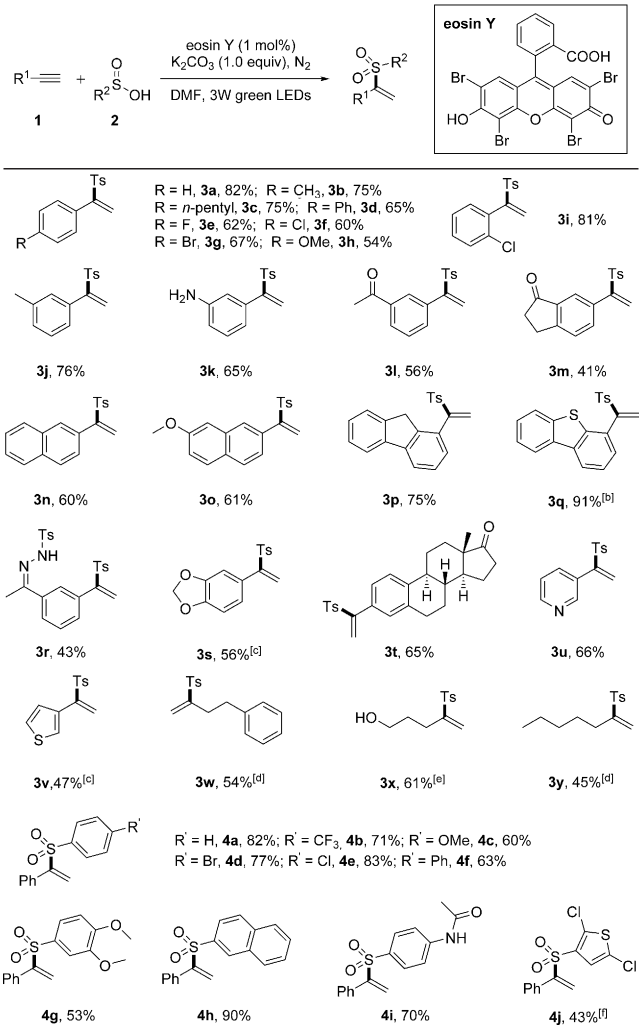
a considerable influence on the efficiency of this transformation (Table S1, entries 5–10). Notably, no desired product was obtained in the absence of photocatalyst or visible light-irradiation (Table S1, entries 13 and 14). After extensive screening of reaction parameters, we found that treatment of **1a** with **2a** in the presence of eosin Y as photoredox catalyst and K_2CO_3 as the base in DMF at room temperature afforded **3a** in 86% yield with high α-regioselectivity.

With the optimal reaction conditions in hand, we next examined the radical Markovnikov addition protocol for the synthesis of α-substituted vinyl sulfones. As shown in Table 1, the transformation was applicable to various terminal alkynes, giving the Markovnikov products in moderate to good yields. Aromatic alkynes, bearing various functional groups at the *para* position, reacted smoothly with *p*-toluenesulfinic acid to afford the desired products (**3a**–**3h**). Interestingly, aromatic alkynes with substituents at the *ortho* position also proceeded smoothly to give the α-vinyl sulfones in 81% yield (**3i**). Moreover, a range of functional groups, including halides (F, Cl, Br), carbonyl, and even sulfonamide, were available for this transformation. More importantly, the reaction is compatible with 3-aminophenylacetylene to afford the corresponding product **3k**, which is difficult to synthesize by transition metals catalysis owing to the coordination of amino group to metal. This feature can be introduced to the synthesis of useful compounds bearing a coordinating group. Remarkably, fluorine and dibenzothiophene, being widely used in organic optoelectronic materials,[11] were also efficient coupling partners (**3p** and **3q**). Estrone derivative **3t** was also successfully generated. It is noteworthy that heteroaromatic alkynes were found to be suitable for the transformation, delivering **3u** and **3v** in 66% and 47%, respectively. Finally, aliphatic alkynes, such as phenylbutyne, 4-pentyn-1-ol, 1-heptyne and so on, provided moderate yields (**3w**–**3y**). Among them, **3x** could be synthesized in 61% yield without the use of protecting groups.

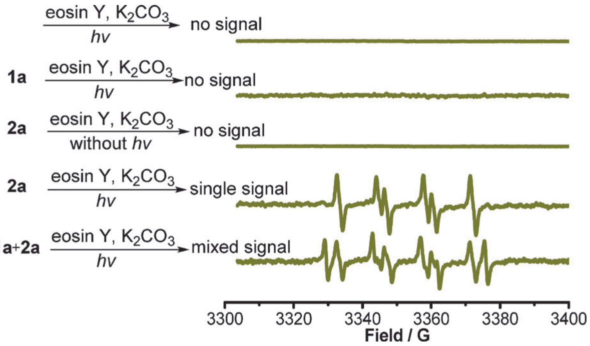
Table 1: Substrates scope for synthesis of α-vinyl sulfones.[a]



[a] Isolated yields are shown. Unless otherwise noted, the standard conditions were as follows: **1** (0.3 mmol), **2** (0.6 mmol), eosin Y (1 mol%), K_2CO_3 (1.0 equiv), DMF (4.0 mL), N_2, 3W green LEDs, 4 h. [b] 6 h. [c] 4.5 h. [d] Eosin Y (2 mol%). [e] Eosin Y (2 mol%), Cs_2CO_3 (1.0 equiv). [f] TFA (0.6 mmol), K_2CO_3 (1.0 equiv), 2,5-dichlorothiophene-3-sulfinic acid sodium salt (0.6 mmol).

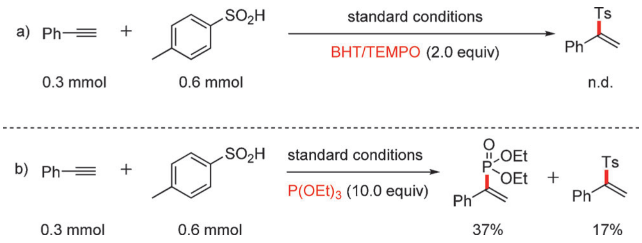
Next, the substrates scope with regard to sulfinic acids was evaluated. As shown in Table 1, the reaction is compatible with a series of sulfinic acids, generating Markovnikov products with good efficiency. Notably, Br and Cl substituents are well tolerated, thus enabling further functionalization (**4d** and **4e**). A good yield was also obtained with the use of naphthalene sulfinic acid as coupling partner (**4h**). Intriguingly, benzenesulfinic acid bearing an acetyl amino group in *para* position was easily transformed (**4i**); the product is difficult to synthesize by other methods. Most importantly, a heterocyclic substrate was a valid coupling partner, affording the desired product (**4j**) in 43% yield.

To elucidate our hypothesis for this visible light-mediated Markovnikov addition of proceeding through a radical cross-coupling process, a series of mechanistic studies were conducted by electron paramagnetic resonance (EPR) spectroscopy, as shown in Scheme 2. Notably, when the reaction mixture of **2a** was irradiated with visible light, a distinct signal of a trapped radical was observed, suggesting the involvement of a sulfonyl radical in the transformation. These results indicated that photocatalysis plays an essential role in the formation of the sulfonyl radical. In further EPR experiments, distinct mixed signals of the trapped radical were detected in the reaction mixtures of **1a** and **2a** under standard conditions, demonstrating that the transformation not only involves



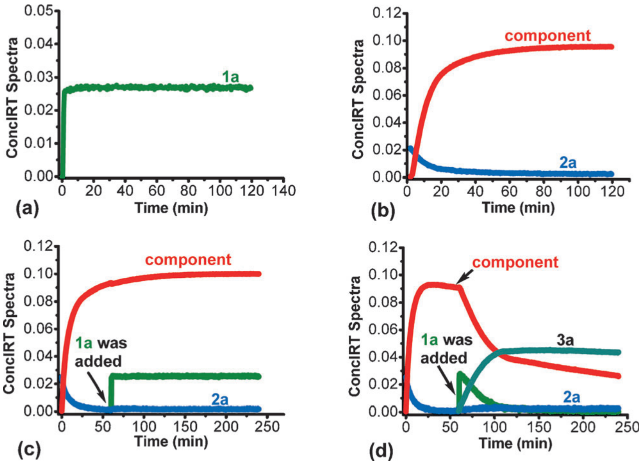
Scheme 2. EPR experiments.

a radical pathway, but also might contain mixed radical species. In addition, radical trapping experiments were also performed (Scheme 3). The reactions were found to be strongly inhibited by radical scavengers, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and 2,4-di-*tert*-butyl-4-methylphenol (BHT), supporting the proposed radical pathway of this reaction. More importantly, α-vinyl carbon radical was trapped by $P(OEt)_3$ in the transformation.[12] Combining the above information, we hypothesized that α-vinyl carbon radical/sulfonyl radical cross-coupling might be the key step in the transformation.



Scheme 3. Radical trapping experiments.

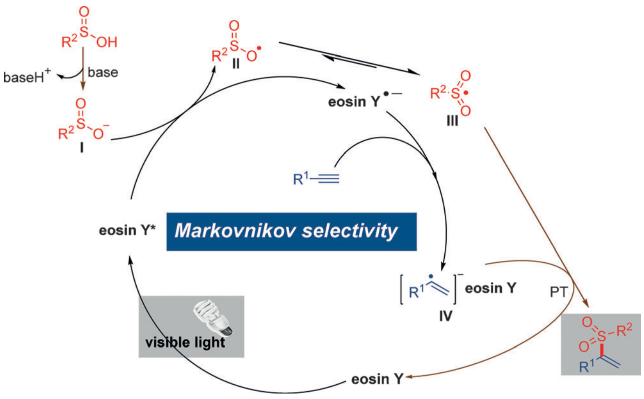
To further investigate the mechanism, operando IR experiments were performed to monitor the reaction, as shown in Scheme 4. No transformation proceeded when **1a** was subjected to the standard reaction condition alone (Scheme 4a). In contrast, when **2a** was subjected to the same reaction conditions a new component was formed, presumably a sulfinate salt based on comparison with sodium *p*-tolylsulfinate (Scheme 4b). To gain deeper insight into the transformation, control experiments in the presence or absence of the visible light were also monitored by operando IR. No further conversion was observed when **1a** was added to the reaction mixture after 1 h in the absence of visible light irradiation (Scheme 4c). In contrast, in the presence of visible light rapid consumption of both **1a** and "component" was detected along with the formation of desired product **3a** (Scheme 4d). These results indicated that visible light is indispensable for the formation of **3a** (see the Supporting Information for details).



Scheme 4. Operando IR experiments. Kinetic profiles for eosin Y (1 mol%), K_2CO_3 (0.3 mmol) in DMF (4.0 mL) under different conditions: a) **1a** (0.3 mmol), under visible light; b) **2a** (0.6 mmol), under visible light; c) **2a** (0.6 mmol), addition of **1a** (0.3 mmol) after 1 h without visible light; d) **2a** (0.6 mmol), addition of **1a** (0.3 mmol) after 1 h under visible light.

Additionally, intermediate experiments were carried out (see SI for further details). First, the reaction of β-substituted vinyl sulfone **4** under standard conditions was investigated. However, no further conversion from **4** to the desired product **3a** was detected. Furthermore, **4** and **2a** did not react to afford the desired product **3a**. Similarly, **1a** and thiosulfonate **5** did not react to generate **3a**. These results rule out the possibility of **4** and **5** as intermediates of this transformation en route to α-substituted vinyl sulfones.

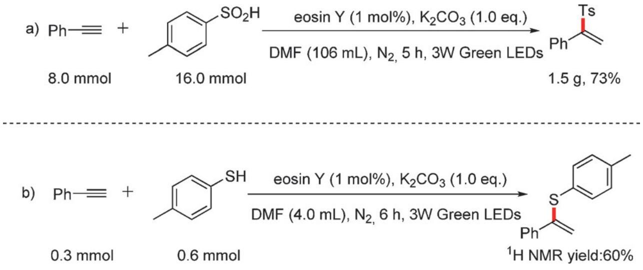
On the basis of these results, a plausible mechanism of visible light-mediated Markovnikov addition of sulfonyl radical to terminal alkynes is illustrated in Scheme 5. First, sulfinate **I** is generated from acid–base neutralization reaction between sulfinic acid with base. Subsequently, the excited state of eosin Y reacts with **I** to afford intermediate **II** along with the formation of eosin Y$^{\bullet -}$, and intermediate **II** resonates to intermediate **III**. Then, eosin Y$^{\bullet -}$ reacts with alkyne to induce the formation of an α-vinyl carbon radical intermediate. Finally, the Markovnikov product is formed via α-vinyl carbon radical/sulfonyl radical cross-coupling and proton transfer (PT).



Scheme 5. Tentative mechanism.

To verify the usefulness of this Markovnikov addition protocol, the phenylacetylene reaction was scaled up to 8 mmol. The procedure proceed smoothly, giving the desired product in 73% yield (Scheme 6a), which demonstrated that the protocol opens up an opportunity to generate biologically active compounds having α-substituted vinyl sulfone structural scaffolds on a larger scale. Pleasingly, this addition protocol was also applicable to the construction of α-substituted vinyl sulfides which are widely used in the synthesis of natural products and pharmaceuticals (Scheme 6b).[13,14]

In summary, we have developed a transition-metal-free, visible light-mediated radical Markovnikov addition for the



Scheme 6. a) Reaction scale-up. b) Expansion of the reaction scope to vinyl sulfides.

highly regioselective synthesis of α-substituted vinyl sulfones via α-vinyl carbon radical/sulfonyl radical cross-coupling. The method exhibits broad functional-groups tolerance and can be extended to larger scale. Pleasingly, the novel strategy is also available for the construction of α-substituted vinyl sulfides. This protocol provides not only a practical methodology for the synthesis of α-substituted vinyl compounds from simple starting materials, but also allows to control regioselectivity in radical additions to terminal alkynes. Ongoing research including further mechanistic details and expanding the methodology to other heteroatom substrates are currently underway.

Experimental Section

General procedure for the synthesis of α-substituted vinyl sulfones: A mixture of phenylacetylene (**1a**, 0.3 mmol), *p*-toluenesulfinic acid (**2a**, 0.6 mmol), K_2CO_3 (0.3 mmol), eosin Y (1.0 mol%) in degased dry DMF (4.0 mL) was stirred under an argon atmosphere and irradiated with commercially available 3 W green LED for 4 h. Then, water was added and the mixture was extracted with ethyl acetate (×4). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude product was separated on a silica gel column with hexane and ethyl acetate as eluent to afford the desired product.

Acknowledgements

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Keywords: Markovnikov selectivity · photoredox catalysis · radical addition · radical cross coupling · transition-metal-free synthesis

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Communications

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H. Wang, Q. Lu, C. Chiang, Y. Luo,
J. Zhou, G. Wang, A. Lei* ____ ■■■■–■■■■

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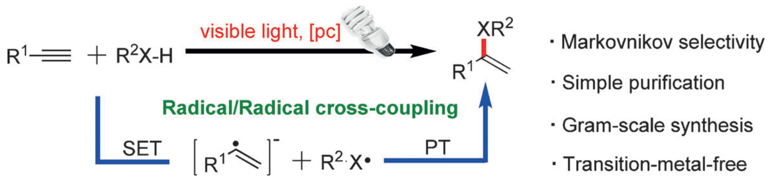

A transition-metal-free, visible light-mediated radical Markovnikov addition was developed enabling the highly regioselective synthesis of α-substituted vinyl sulfones through a radical–radical cross-coupling process. The reaction shows good functional-groups tolerance and can be easily scaled-up.