

Letter

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Z-Selective Addition of Diaryl Phosphine Oxides to Alkynes via Photoredox Catalysis

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ABSTRACT: Radical addition to alkynes is known to yield predominantly thermodynamically more stable E-alkenes. Control of stereoselectivity in these reactions, and the isolation of the higher energy Z-alkenes remain an important challenge in chemical synthesis. Herein, direct synthesis of Z-alkenylphosphine oxides via visible-light-induced radical addition to alkynes in water is reported. This protocol was effective with various terminal and internal alkynes, affording products with high Z stereoselectivity. Moreover, this transformation was demonstrated on gram scale. Mechanistic studies support the following conclusions: 1) the reaction proceeds via free-radical addition; 2) the choice of K_2CO_3 as aqueous base is crucial to the transformation; 3) π - π stacking interaction greatly improves Z selectivity.

KEYWORDS: Z selectivity • π - π stacking interaction • terminal and internal alkynes • gram-scale synthesis • radical addition

Z-alkenes are fundamental structures in a series of biologically active natural products.¹ Classical methods for the synthesis of such molecules include the Wittig reaction,² catalytic alkyne hydrogenation,³ cross-metathesis,^{1b, 4} and coupling reaction.⁵ Apart from these well-established processes, addition reactions to alkynes offer a more straightforward, atom-economical, and environmentally benign alternative to these traditional approaches.⁶ Although the good reactivities in these reactions are achieved, the stereoselective control, especially Z-selectivity, remains challenging. Recently, transition-metal-catalyzed addition reactions to terminal alkynes have emerged as a powerful tool to access Z-alkenes (Scheme, 1a).⁷ In this regard, the use of electron-rich, and specific bulky ligands within complexes based on iron,^{7a, 7f} cobalt,^{7e, 7g} and ruthenium^{7h} shows promising selectivity, giving rise to previously inaccessible Z-alkenes. Nevertheless, in most examples, in situ generation of a metal acetylide from the oxidative addition between metal and terminal alkyne results in the inapplicability of internal alkynes in some way.^{7a-7h} In 2013, ruthenium-catalyzed hydroboration of internal alkenes was reported⁷ⁱ. Thus, a simple and efficient approach to forming Z-alkenes via addition to alkynes, especially internal alkynes, remains highly desirable yet challenging.

Very recently, direct radical addition to alkynes has become a good alternative approach to synthesizing functionalized alkenes.⁸ Nevertheless, there are a series of uncontrollable factors, such as a steric effect⁸ and the Kharasch effect⁹, leading to the difficulty of the control of the regioselectivity. In principle, a linearized alkenyl radical is generally obtained because of either resonance stabilization or hyperconjugation. Lower energy E-alkenes are normally formed in most of the radical addition to alkynes. On the contrary, the art for synthesis of Z-alkenes via radical addition to alkynes is at a primitive stage (Scheme. 1b).¹⁰



Scheme 1 Synthesis of Z-alkenes via radical addition to alkynes.

Z-alkenylphosphine oxides have versatile synthetic application in chemical synthesis.¹¹ To date, the existing

methods for generation of the Z-alkenylphosphine oxides suffer from labor-intensive multistep operations, low selectivity, or limited scope.¹² In this context, addition of P(0)-H bonds to alkynes is a straightforward and atom-economical strategy to access alkenylphosphine oxides.^{12e-g} Despite the significance of these developments, controlling of Z selectivity remains a fundamental challenge, especially in radical addition reaction. Considering the wide use of photocatalysis in radical reactions,¹³ we envisioned that photocatalysis is a worthwhile method to achieve the hydrophosphonylation of alkynes via a radical process. Herein, we report a visible-light-induced and transition-metal-free protocol to synthesize Z-alkenylphosphine oxides via a radical addition to alkynes in water at room temperature. Importantly, terminal alkynes and internal alkynes were amenable to this transformation. With respect to aromatic alkynes, the additional π - π stacking interaction with the phosphorus substituents has been shown to improve the Z selectivity (Scheme 1c).

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Initially, diphenylphosphine oxide (2a) was selected as a model substrate for reaction with phenylacetylene (1a) (Supporting Information, Table S1). Eosin Y was chosen as a photosensitizer.¹⁴ Pleasingly, after a screening of reaction parameters, the desired product (3a) was obtained in 65% yield and high Z selectivity (Z:E=96:4) with the use of H₂O as the solvent, eosin Y as photosensitizer, and K₂CO₃ as base. It is noteworthy that no Markovnikov products were detected in this transformation. Control experiments were performed to elucidate the role of each reactant. Water proved to be the optimal solvent for this transformation, possibly owing to the hydrophobic effect.¹⁵ On the contrary, organic solvents showed much lower efficiency and regioselectivity. In comparison with organic bases, K₂CO₃ promoted the transformation most efficiently. Changing the catalyst loading offered relatively unchanged yields and high regioselectivity. Moreover, changing the amount of 2a was unsuccessful to improve the yield of the reaction. Most importantly, only a trace amount of desired product was detected in the absence of either eosin Y or the irradiation of visible light, both of which play an essential role in the generation of the phosphinoyl radical.

39 With the optimal conditions in hand, we investigated the 40 efficiency of this visible-light-induced Z-selective protocol. 41 As shown in Table 1, the envisioned stereoselectivity and 42 moderate to good yields were observed when various terminal alkynes reacted with diphenylphosphine oxide (2a). 43 Electron-donating or electron-withdrawing para-substi-44 tuted phenylacetylenes were amenable to this protocol, af-45 fording the desired products with high Z selectivity (3b and 46 3c). Halogen groups such as F, Cl, and Br were also compat-47 ible with this transformation (3d, 3e, and 3f). Additionally, 48 alkyne containing a hydroxyl group was a good coupling 49 partner to form the desired product 3g, which can translate 50 into ester derivatives via esterification of hydroxyl group. 51 Then, meta-substituted phenylacetylenes were investigated. 52 3, 5-Methoxyl substituted alkyne reacted well with diphe-53 nylphosphine oxide to (2a) form the desired product (3h). 54 Moreover, phenylacetylenes containing halogen groups 55 were good reaction partners (3j and 3k). It is noteworthy 56 that amide and sulfonamide groups could afford the desired products (31-30). Surprisingly, ortho-substituted aryl 57

alkynes were also suitable reaction partners, furnishing desired products with higher Z selectivity in spite of unfavorable steric hindrance (**3p-3r**). With regard to aliphatic alkynes, an increase in the loading of eosin Y and longer time were necessary, and lower Z selectivity was observed in comparison to aryl acetylene.

Table 1: Substrate scope^a



^aCondition: alkynes 1 (0.3 mmol), diphenylphosphine oxides 2 (0.6

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mmol), eosin Y (1 mol%), K2CO3 (1.0 equiv), H2O (4.0 mL), N2, 12 h, 3 W green LEDs. ^b24 h, ^c48 h, ^deosin Y (1.5 mol%), 24 h. ^eeosin Y (1.5 mol%), 48 h. ^fdiphenylphosphine oxide (1.2 mmol), 24 h.

The reaction protocol allowed 1-heptyne to react well with diphenylphosphine oxide (2a) to provide desired product (3s). Aliphatic alkynes containing either a hydroxyl group or an amino group could provide desired products 6 with moderate yields (3t and 3v), which exhibit good functional group tolerance. Most importantly, internal alkynes 8 were compatible with this protocol. 1-Phenyl-1-propyne 9 and 1-Phenyl-1-butyne could react with diphenylphosphine 10 oxide (2a) to access the desired compounds (3w and 3x), 11 which could not be synthesized through transition-metal-12 catalyzed addition reaction of alkynes.7a-7h However, when 13 we used diphenylacetylene as reaction partner, only trace 14 amount of addition product was detected because of steric hindrance. Moreover, 3-phenyl-2-propyn-1-ol containing 15 electron-donating or electron-withdrawing groups were 16 widely studied. Corresponding products (3y-3ac) were di-17 rectly obtained with good Z selectivity via this visible-light-18 induced protocol, avoiding multistep operations and use of 19 hazardous reagents.^{12d} Next, the scopes of the phosphine 20 oxides were also tested with the use of phenylacetylene as 21 coupling partner. Phosphine oxides bearing methxyl, meth-22 oxyl, fluoric, and difluoro groups afforded the desired prod-23 ucts with high Z selectivity (3ae-3ah). However, diethyl 24 phosphite could not react with phenylacetylene to provide 25 the desired product (3ai). We speculated that diethyl phos-26 phite might be difficult to be oxidized under standard con-27 ditions because of its higher oxidative potential than diphenylphosphine oxide.¹⁸ Gratifyingly, this visible-light-in-28 duced Z-selective protocol was compatible with a series of 29 amino acid substrates, affording corresponding products in 30 moderate yields (3aj-3al), which further demonstrates 31 good functional group tolerance of this protocol. In addition, 32 gram-scale synthesis was conducted (Scheme 2). To our de-33 light, 52% yield and decent Z selectivity was observed when 34 the reaction was carried out on 8 mmol scale in water. The 35 results highlight not only the good functional group toler-36 ance but also the potential applications of this protocol in 37 the large-scale synthesis. 38

$$Ph = + H + P_{Ph} + H + P_{Ph} + P_{Ph} + H_{2} + P_{2} + P_$$

Scheme 2 Large-scale synthesis

According to the literature,16 E-alkenes have the possibility of being converted into less stable Z-isomers under the irradiation of the visible light. To investigate the mechanism in detail, some experiments were performed (Scheme 3). No conversion was detected when Ealkenylphosphine oxide (4a) was added to the system, excluding the possibility of E-alkenylphosphine oxide (4a) as an intermediate in this visible-light-induced Z-selective protocol (Scheme 3a). Subsequently, radical trapping experiments were conducted. The transformation was strongly inhibited in the presence of the 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), demonstrating the reaction might involve a radical pathway (Scheme 3b). To confirm the radical process, allyl ether (5) was used as a coupling

partner to react with 2a under standard conditions. As shown in Scheme 3b. 6 was obtained in 58% vield, suggesting the existence of phosphinoyl radical in this transformation.¹⁷ Then, EPR experiments were performed (Scheme 4). A distinct EPR signal was detected when free radical spin trapping agent DMPO was added to the system. The parameters observed for the spin adduct are g=2.0065, a_N=14.17 G, α_H =18.92 G, α_P =36.22 G. We assumed the relatively stable radical belongs to A¹⁸ further showing the presence of phosphinoyl radical in this transformation (Scheme 4a). Similarly, the same signal was detected when diphenylphosphine oxide was used as the only substrate under the standard conditions (Scheme 4b). However, no signal was detected in the absence of the either eosin Y or K₂CO₃ (Scheme 4c, 4d). Moreover, time profile of this reaction confirms the indispensability of visible light, suggesting that continuous visible-light irradiation is necessary for the synthesis of Z-alkenylphosphine oxides (For detail, see Supporting Information, Scheme S1).



Scheme 3 Mechanistic studies





Scheme 4 EPR experiments. Standard reaction conditions: phenylacetylene (1a, 0.3 mmol), diphenylphosphine oxide (2a, 0.6 mmol), eosin Y (1 mol%), K2CO3 (1.0 equiv), DMPO (20 uL), H2O (4.0 mL), N₂, 3 W green LEDs, 10 min.

Page 4 of 7



Scheme 5 Deuterium labeling experiment.

To evaluate the origination of the α -proton in the vinyl group of **3a**, deuterium labeling experiments were performed (Scheme 5). 3a-2D rather than 3a or 3a-D could be obtained under the standard conditions in D₂O (Scheme 5a). Only 20% yield of **3a-2D** was detected, which might be due to the higher energy of deuteron abstraction from D₂O (Scheme 5a). Along with the extension of time, the yield of the reaction could increase (Scheme 5a). Moreover, neither 3a-2D nor 3a-D was detected when 3a was added to the standard reaction system, ruling out the possibility of the transformation from 3a to 3a-2D in D₂O (Scheme 5b). Finally, only 1a-D was detected under standard conditions (Scheme 5c), suggesting the β -deuteron of **3a-2D** (in Scheme 5a) comes from 1a-D which was generated in situ during the reaction. According to the above results, we propose the α -proton in the vinyl group of **3a** comes from water.

Subsequently, to understand the effect of K_2CO_3 in this reaction, UV experiments were conducted to investigate the interaction between K_2CO_3 and eosin Y. As shown in Scheme 6, the absorbance significantly increased as the amount of K_2CO_3 raised. In accordance with Beer-Lambert Law (A = Kbc), the result suggests that K_2CO_3 could accelerate the dissolution of photosensitizer in water via acid-base reaction.



Scheme 6 UV-vis absorption spectra of systems containing (1) K_2CO_3 (10⁻⁵ M); (2) eosinY (10⁻⁵ M); (3) eosinY (10⁻⁵ M), K_2CO_3 (2 x 10⁻⁶ M); (4) eosinY (10⁻⁵ M), K_2CO_3 (6 x 10⁻⁶ M); (5) eosinY (10⁻⁵ M), K_2CO_3 (10⁻⁵ M); (6) eosinY (10⁻⁵ M), K_2CO_3 (3 x 10⁻⁵ M), and in water. λ max=517 nm.

Based on the above results, we proposed a tentative mechanism for this Z-selective protocol, which is shown in Scheme 7. Firstly, a phosphinoyl radical (I) is formed via proton-coupled electron transfer (PCET) oxidation in the presence of photoexcited catalysts.¹⁹ Secondly, a phosphinoyl radical reacts with phenylacetylene, affording the α -alkenyl carbon radical (II). Then, PC • attacks the linear radical (II), delivering Z-alkenyl anion (III) via single-electron transfer. In this process, we propose that π - π stacking interaction of the aromatic ring of the phenylacetylene and diphenylphosphine oxide greatly improves Z selectivity. Notably, an X-ray single-crystal structure of 3ad was obtained. As shown in Scheme 7, one of the aromatic ring of diphenylphosphine oxide and pyridine are on the same side, suggesting the existence of the π - π stacking interaction between aromatic rings.^{20,21} Finally, Z-alkenylphosphine oxides can be obtained via a proton transfer to Z-alkenyl anion (III).



Scheme 7 Proposed mechanism.

In conclusion, we have developed a visible-light-induced and transition-metal-free protocol to synthesize Zalkenylphosphine oxides via radical addition to alkynes at room temperature. The reaction features high Z selectivity, the use of water as solvent, broad functional-groups tolerance, and gram-scale synthesis. Pleasingly, the internal alkynes are also suitable coupling partners to react with diphenylphosphine oxide to offer alkenes with high Z selectivity. This work not only offers an efficient approach to the formation of Z-alkenylphosphine oxides, but also provides a guide for the control of the stereoselectivity in radical addition chemistry. Ongoing researches including further mechanism and scopes are currently underway.

ASSOCIATED CONTENT

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57 58 **Supporting Information.** Experiment details and spectral data for all compounds are provided. This material is availa-ble free of charge via the Internet at <u>http://pubs.acs.org</u>.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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