Catalysis Science & Technology

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/catalysis

Journal Name

COMMUNICATION

Metal-free Oxidative Phosphinylation of Aryl Alkynes to β-Ketophosphine Oxides *via* Visible-Light Photoredox Catalysis†

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Mei-jie Bu, Guo-ping Lu and Chun Cai*

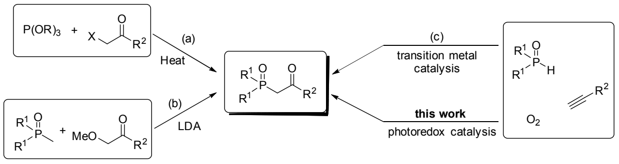
A method for photocatalytic oxidative coupling of diaryl phosphine oxides and arylacetylenes under mild conditions was developed. Rhodamine B, an inexpensive and commercially available organic dye, was used as the photocatalyst. This protocol realizes a regioselective 1,2-difunctionalization of arylacetylenes and provides a metal-free access toward a series of β-ketophosphine oxides.

The construction of carbon–phosphorus bonds is synthetically important, because organophosphorus compounds are an important class of chemicals that have broad utilities as reagents for organic synthesis,[1] ligands for transition metal catalysts,[2] pharmaceuticals,[3] and functional materials.[4] In particular, β-ketophosphine oxides, which can be applied in the Horner-Wadsworth-Emmons reactions,[5] are typical structures of organophosphorus compounds. Traditionally, β-ketophosphine oxides are prepared by Arbuzov reaction, which involves the reactions between α-haloketones with trialkylphosphites,[6] and the reaction often requires high temperature (Scheme 1a). Acylation of alkylphosphine oxides provides another reliable approach to β-ketophosphine oxides,[7] however, stoichiometric amounts of the hazardous organometallic reagents are needed in this protocol (Scheme 1b). Other approaches, hydration of alkynylphosphine oxides[8] and oxidation of β-hydroxyalkylphosphines,[9] suffer limitations like inaccessible materials and tedious procedures.

Difunctionalization of alkynes is currently an attractive strategy. It allows the introduction of two functional groups in a single stroke. Oxidative phosphinylation of alkynes can efficiently afford β-ketophosphine oxides in one step from simple starting materials, and this method could be put into practice using transition metal catalysis. Oxidation of secondary phosphine oxide (SPO) by silver,[10] copper,[11] or manganese[12] could afford P-centered radical, which is a highly reactive phosphinylation reagent. Recently, a silver/copper catalysis system was demonstrated to be effective for the direct oxidative phosphinylation of alkynes with oxygen in the air.[10b] Almost at the same time, He[11c] and Song[11d] reported the copper/iron-catalyzed reactions for the formation of β-ketophosphine oxides, respectively (Scheme 1c). Although existing methods are undoubtedly useful, the development of a more environmentally benign method to produce β-ketophosphine oxides is still highly desirable in modern organic chemistry.

The past several years have witnessed a rapid, prominent development of visible-light photoredox catalysis,[13] which is highly desirable from the viewpoint of energy saving and environmental friendliness. And efforts have been made by several groups for the construction of C–P bonds facilitated by visible-light photocatalysis.[14] In fact, reductive quenching of the excited state of photocatalyst with SPO could generate the phosphorus radical. In 2013, Kobayashi introduced this elegant method for the first time, and applied the method to the hydrophosphinylation of unactivated alkenes.[15] Later, a similar strategy was used by Lu and Xiao for the arylation of SPOs by combining nickel catalysis and visible-light-induced photoredox catalysis.[16] We hypothesized that the P-centered radicals generated in this manner might also engage in oxidative couplings with aryl alkynes to realize a regioselective difunctionalization of arylacetylenes for the generation of β-ketophosphine oxides (Scheme 1).

To this end, we began our investigations with the oxidative coupling between diphenylphosphine oxide **1a** and phenylacetylene **2a**. When the experiment was catalyzed by $Ru(bpy)_3Cl_2 \cdot 6H_2O$, one of the most commonly employed visible-light photocatalysts, and irradiated with a white LED lamp in isopropanol under O_2 at room temperature, the desired

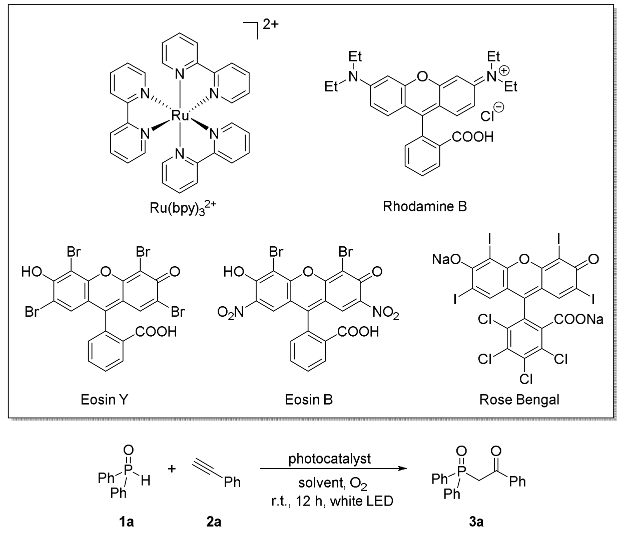


Scheme 1 General routes to β-ketophosphine oxides.

Chemical Engineering College, Nanjing University of Science and Technology, Nanjing, Jiangsu 210094, P. R. China. E-mail: c.cai@mail.njust.edu.cn; Fax: (+86)-25-8431-5030; Tel: (+86)-25-8431-5514.

† Electronic Supplementary Information (ESI) available: Experimental procedures for the synthesis, spectral data and NMR spectra. See DOI: 10.1039/x0xx00000x

Table 1 Optimization studies[a]



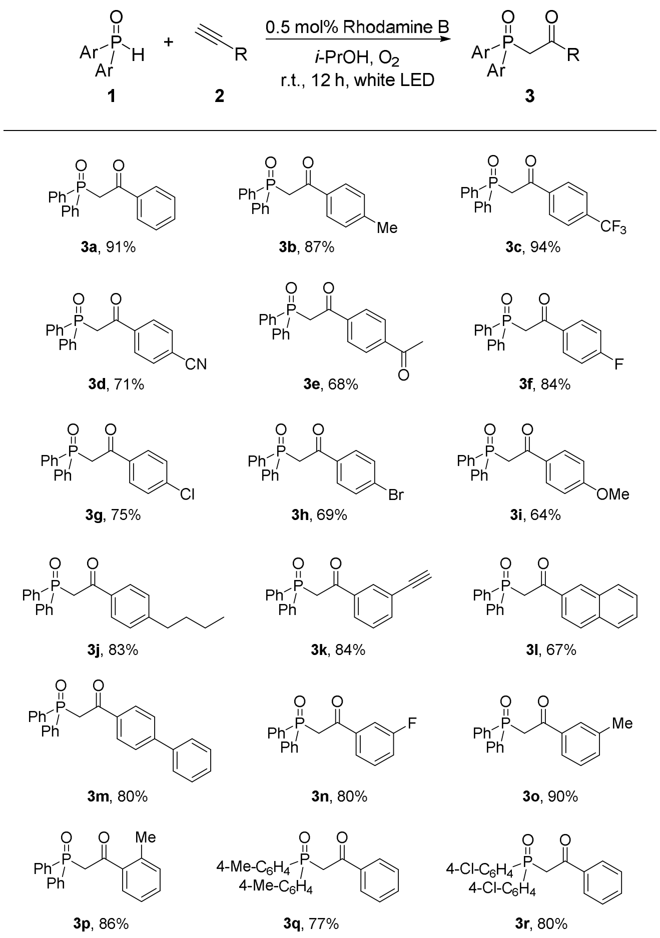
Entry	Catalyst	Solvent	Yield (%)[b]
1	$Ru(bpy)_3Cl_2 \cdot 6H_2O$ (2 mol%)	*i*-PrOH	52
2	Rhodamine B (2 mol%)	*i*-PrOH	79
3	Eosin Y (2 mol%)	*i*-PrOH	68
4	Eosin B (2 mol%)	*i*-PrOH	45
5	Rose Bengal (2 mol%)	*i*-PrOH	30
6	Rhodamine B (0.5 mol%)	*i*-PrOH	91
7	Rhodamine B (0.5 mol%)	CH_3OH	67
8	Rhodamine B (0.5 mol%)	EtOH	83
9	Rhodamine B (0.5 mol%)	CH_3CN	85
10	Rhodamine B (0.5 mol%)	THF	83
11	Rhodamine B (0.5 mol%)	DCM	59
12	Rhodamine B (0.5 mol%)	DMF	77
13	Rhodamine B (0.5 mol%)	DMSO	67
14[c]	Rhodamine B (0.5 mol%)	*i*-PrOH	75
15	None	*i*-PrOH	trace

[a] Reaction conditions: **1a** (0.4 mmol), **2a** (1.2 mmol), photocatalyst, solvent (0.4 mL), irradiation with a white LED lamp under an oxygen atmosphere at r.t. for 12 h. [b] Isolated yields of product **3a**. [c] The reaction was conducted in the air.

product **3a** was obtained in 52% yield after a reaction time of 12 hours (Table 1, entry 1). As an alternative to transition metal complexes in photoredox catalysts, organic dyes are less expensive and less toxic.[13g, 17] So we evaluated some organic dyes, and the results indicated that the best photocatalyst for this reaction was rhodamine B (Table 1, entry 2), which was also employed in Kobayashi's report as photocatalyst for the generation of P-centered radicals.[15] Then, the catalyst loading was cut to 0.5 mol%, which resulted in an improved yield of 91% (Table 1, entry 6).[18] Finally, different solvents were screened, and isopropanol remained to be the best for the oxidative phosphinylation. When the experiment was directly exposed to air, the yield declined to 75% (Table 1, entry 14). When no phtotocatalyst was added, the reaction became sluggish and trace product was observed after the reaction time (Table 1, entry 15).

With the optimized conditions in hand,‡ this approach was then applied to the reaction of SPO **1a** and a variety of aryl alkynes, the results of which are summarized in Table 2. Various aryl alkynes carrying electron-donating and -withdrawing substituents at the *para* position could successfully react with diphenylphosphine oxide to give the targeted products. Arylacetylenes bearing halogen substituents (**2f-h**, **2n**) on the aromatic ring all gave the corresponding products with an intact carbon-halogen bond, which can be used for further transformation in transition-metal catalyzed reactions. *Ortho* and *meta*-substituents at the aryl moiety were also tolerated (**3n-p**). Moderate yield was gained with the naphthyl derivative (**2l**), and 4-ethynyl-1,1'-biphenyl (**2m**) also worked well. It is worth noting that only one ethynyl group reacted with **1a** in 1,3-diethynylbenzene (**2k**). However, products were not detected with 3-ethynylaniline and ethynylcyclohexane. The reactions of SPO **1a** with internal alkynes, 1-phenyl-1-propyne and 1-phenyl-1-butyne, both resulted in a complex mixture, and the products could not be separated.

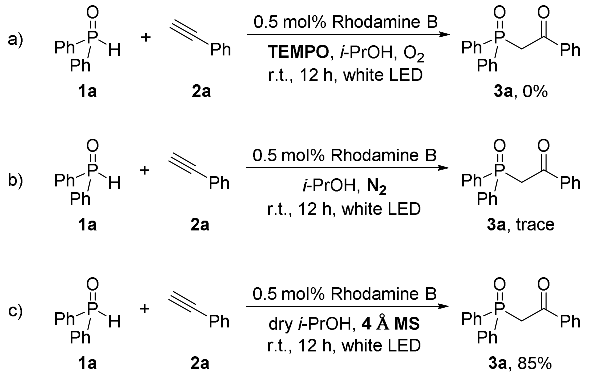
Table 2 Scope of the photocatalytic oxidative phosphinylation[a]



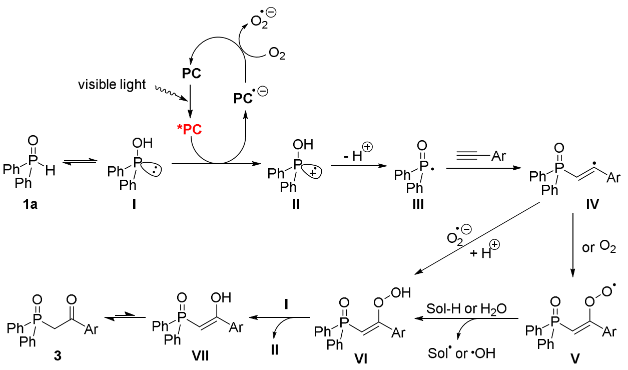
3a, 91% **3b**, 87% **3c**, 94%
3d, 71% **3e**, 68% **3f**, 84%
3g, 75% **3h**, 69% **3i**, 64%
3j, 83% **3k**, 84% **3l**, 67%
3m, 80% **3n**, 80% **3o**, 90%
3p, 86% **3q**, 77% **3r**, 80%

[a] Reaction conditions: **1** (0.4 mmol), **2** (1.2 mmol), rhodamine B (0.5 mol%), solvent (0.4 mL), irradiation with a white LED lamp under an oxygen atmosphere at r.t. for 12 h. Isolated yields.

Two other electron-rich SPOs were also surveyed to



Scheme 2 Experiments for the mechanistic study.



Scheme 3 Possible mechanism.

investigate the scope of the reaction. To our delight, the reactions with phenylacetylene **2a** afforded the corresponding products (**3q**, **3r**) with the yields of 77% and 80%.

Some control experiments were conducted to gain insight into the mechanism. When the photocatalytic reaction was performed in the presence of 1.5 equivalents of the radical scavenger 2,2,6,6-tetramethyl-1-piperidin-1-oxyl (TEMPO), it was completely restrained (Scheme 2a), thus indicating a possible radical process. And when this experiment was carried out in a nitrogen atmosphere, trace product was obtained (Scheme 2b), suggesting this protocol requires the presence of oxygen. The reaction conducted under anhydrous conditions gave β-ketophosphine oxide **3a** in 85% yield (Scheme 2c).[19] These two results indicated that oxygen in the product came from O_2.

On the basis of the experiment results and previous reports,[10b, 15, 16] a plausible mechanism for this photocatalytic oxidative phosphinylation was proposed (Scheme 3). SPO **1a** exists in equilibrium with its trivalent tautomer phosphinous acid **I**. Initially, the photoexcited rhodamine B should undergo a single electron transfer (SET) with electron-rich phosphinous acid **I** to produce the corresponding radical-cation intermediate **II**. The rhodamine B radical anion would be quenched by oxygen and ready for the next photocatalytic cycle. Deprotonation of **II** results the formation of P-centered radical **III**. Addition of this P-centered radical to arylacetylene gives alkenyl radical **IV**, which would react with an O_2 radical anion to generate hydroperoxide **VI**,[20] or react with dioxygen to afford peroxy radical **V**. Peroxy radical **V** would convert into hydroperoxide **VI** by H-abstraction from the solvent. The reaction of **VI** with **IV** could result in the homolysis of the oxygen-oxygen bond. Upon the homolysis, hydroperoxide **VI** reacts with phosphinous acid **I** to generate another molecule of **II**, along with the enol **VII**. Finally, product **3** is afforded *via* a quick tautomerization. It's crucial that singlet oxygen should not be produced by excited-state photocatalyst *via* energy transfer, because it tends to react with most alkynes. Thus, rhodamine B should be suitable and efficient for this reaction.[21]

In conclusion, we have developed an oxidative phosphinylation of aryl alkynes under aerobic conditions facilitated by visible light. With a low catalyst loading of rhodamine B, these reactions proceed smoothly under mild conditions *via* a radical process and provide a wide range of β-ketophosphine oxides in good yields. This protocol is metal-free and operationally simple, using an inexpensive organic dye as the photocatalyst and visible light as a green source of energy.

Acknowledgements

We acknowledge financial support from Jiangsu Natural Science Foundation (BK 20131346).

Notes and references

‡ The photocatalytic reactions were irradiated with a 23W household white LED lamp which was directly got from the supermarket. A 10 mL reaction vessel was equipped with rhodamine B (1 mg, 0.002 mmol, 0.5 mol%), SPO **1** (0.4 mmol) and a magnetic stirring bar. *i*-PrOH (0.4 mL) was added, followed by aryl alkyne **2** (1.2 mmol, 3 equiv.). The mixture was irradiated with the white LED lamp and stirred under O_2 (balloon) at room temperature for 12 h. After the reaction, the reaction was quenched by 10 mL ethyl acetate. The resulting mixture was passed through a plug of silica gel, concentrated under reduced pressure. Purification of the crude product was achieved by column chromatography or preparative TLC. ^{1}H, ^{13}C, ^{31}P and ^{19}F NMR spectra were recorded on an AVANCE III 500 Bruker spectrometer operating at 500 MHz, 125 MHz, 202 MHz and 470 MHz, respectively.

1 (a) J. Boutagy and R. Thomas, *Chem. Rev.*, 1974, **74**, 87; (b) B. E. Maryanoff and A. B. Reitz, *Chem. Rev.*, 1989, **89**, 863; (c) X.-Q. Pan, J.-P. Zou, W.-B. Yi and W. Zhang, *Tetrahedron*, 2015, **71**, 7481; (d) A. R. Choudhury and S. Mukherjee, *Adv. Synth. Catal.*, 2013, **355**, 1989; (e) X.-T. Ma, Y. Wang, R.-H. Dai, C.-R. Liu and S.-K. Tian, *J. Org. Chem.*, 2013, **78**, 11071.

2 (a) H. A. McManus and P. J. Guiry, *Chem. Rev.*, 2004, **104**, 4151; (b) D. J. Gorin, B. D. Sherry and F. D. Toste, *Chem. Rev.*, 2008, **108**, 3351; (c) M.-N. Birkholz, Z. Freixa and P. W. N. M. van Leeuwen, *Chem. Soc. Rev.*, 2009, **38**, 1099.

3 (a) T. S. Kumar, S.-Y. Zhou, B. V. Joshi, R. Balasubramanian, T. Yang, B. T. Liang and K. A. Jacobson, *J. Med. Chem.*, 2010, **53**, 2562; (b) W. Feng, X.-Y. Teo, W. Novera, P. M. Ramanujulu, D. Liang, D. Huang, P. K.

Moore, L.-W. Deng and B. W. Dymock, *J. Med. Chem.*, 2015, **58**, 6456; (c) L. Weinschenk, D. Schols, J. Balzarini and C. Meier, *J. Med. Chem.*, 2015, **58**, 6114.
4 (a) T. Baumgartner and R. Réau, *Chem. Rev.*, 2006, **106**, 4681; (b) S. O. Jeon and J. Y. Lee, *J. Mater. Chem.*, 2012, **22**, 7239; (c) Y. J. Cho and J. Y. Lee, *Chem. – Eur. J.*, 2011, **17**, 11415.
5 (a) L. Horner, H. Hoffmann and H. G. Wippel, *Chem. Ber.*, 1958, **91**, 61; (b) L. Horner, H. Hoffmann, H. G. Wippel and G. Klahre, *Chem. Ber.*, 1959, **92**, 2499; (c) W. S. Wadsworth and W. D. Emmons, *J. Am. Chem. Soc.*, 1961, **83**, 1733; (d) J. Boutagy and R. Thomas, *Chem. Rev.*, 1974, **74**, 87.
6 (a) A. Michaelis and R. Kaehne, *Ber. Dtsch. Chem. Ges.*, 1898, **31**, 1048; (b) B. A. Arbusow, *Pure Appl. Chem.*, 1964, **9**, 307; (c) A. K. Bhattacharya and G. Thyagarajan, *Chem. Rev.*, 1981, **81**, 415.
7 (a) R. S. Torr, S. Warren, *J. Chem. Soc. Pak.*, 1979, **1**, 15; (b) K. Narkunan and M. Nagarajan, *J. Org. Chem.*, 1994, **59**, 6386; (c) D. J. Fox, D. S. Pedersen and S. Warren, *Org. Biomol. Chem.*, 2006, **4**, 3102.
8 (a) X. Li, G. Hu, P. Luo, G. Tang, Y. Gao, P. Xu and Y. Zhao, *Adv. Synth. Catal.*, 2012, **354**, 2427; (b) L. Xie, R. Yuan, R. Wang, Z. Peng, J. Xiang and W. He, *Eur. J. Org. Chem.*, 2014, 2668.
9 M. Koprowski, D. Szymańska, A. Bodzioch, B. Marciniak, E. Różycka-Sokołowska and P. Bałczewski, *Tetrahedron*, 2009, **65**, 4017.
10 (a) X.-Q. Chu, Y. Zi, H. Meng, X.-P. Xu and S.-J. Ji, *Chem. Commun.*, 2014, **50**, 7642; (b) B. Zhang, C. G. Daniliuc and A. Studer, *Org. Lett.*, 2014, **16**, 250; (c) X. Chen, X. Li, X.-L. Chen, L.-B. Qu, J.-Y. Chen, K. Sun, Z.-D. Liu, W.-Z. Bi, Y.-Y. Xia, H.-T. Wu and Y.-F. Zhao, *Chem. Commun.*, 2015, **51**, 3846; (d) Z. Li, F. Fan, Z. Zhang, Y. Xiao, D. Liu and Z.-Q. Liu, *RSC Adv.*, 2015, **5**, 27853; (e) Y. F. Zeng, D. H. Tan, W. X. Lv, Q. J. Li and H. G. Wang, *Eur. J. Org. Chem.*, 2015, 4335.
11 (a) J. Ke, Y. Tang, H. Yi, Y. Li, Y. Cheng, C. Liu and A. Lei, *Angew. Chem. Int. Ed.*, 2015, **54**, 6604; (b) P. Zhang, L. Zhang, Y. Gao, J. Xu, H. Fang, G. Tang and Y. Zhao, *Chem. Commun.*, 2015, **51**, 7839; (c) N. Yi, R. Wang, H. Zou, W. He, W. Fu and W. He, *J. Org. Chem.*, 2015, **80**, 5023; (d) M. Zhou, M. Chen, Y. Zhou, K. Yang, J. Su, J. Du and Q. Song, *Org. Lett.*, 2015, **17**, 1786.
12 (a) X.-Q. Pan, J.-P. Zou, G.-L. Zhang and W. Zhang, *Chem. Commun.*, 2010, **46**, 1721; (b) X.-Q. Pan, L. Wang, J.-P. Zou and W. Zhang, *Chem. Commun.*, 2011, **47**, 7875; (c) D.-P. Li, X.-Q. Pan, L.-T. An, J.-P. Zou and W. Zhang, *J. Org. Chem.*, 2014, **79**, 1850; (d) S.-F. Zhou, D.-P. Li, K. Liu, J.-P. Zou and O. T. Asekun, *J. Org. Chem.*, 2015, **80**, 1214; (e) J. Xu, X. Li, Y. Gao, L. Zhang, W. Chen, H. Fang, G. Tang and Y. Zhao, *Chem. Commun.*, 2015, **51**, 11240.
13 Selected recent reviews: (a) T. P. Yoon, M. A. Ischay and J. Du, *Nat. Chem.*, 2010, **2**, 527; (b) J. M. R. Narayanam and C. R. J. Stephenson, *Chem. Soc. Rev.*, 2011, **40**, 102; (c) J. Xuan and W.-J. Xiao, *Angew. Chem. Int. Ed.*, 2012, **51**, 6828; (d) C. K. Prier, D. A. Rankic and D. W. C. MacMillan, *Chem. Rev.*, 2013, **113**, 5322; (e) M. Reckenthäler and A. G. Griesbeck, *Adv. Synth. Catal.*, 2013, **355**, 2727; (f) M. N. Hopkinson, B. Sahoo, J.-L. Li and F. Glorius, *Chem. – Eur. J.*, 2014, **20**, 3874; (g) D. P. Hari and B. Konig, *Chem. Commun.*, 2014, **50**, 6688.
14 (a) M. Rueping, S. Zhu and R. M. Koenigs, *Chem. Commun.*, 2011, **47**, 8679; (b) W.-J. Yoo and S. Kobayashi, *Green Chem.*, 2014, **16**, 2438; (c) Y. He, H. Wu and F. D. Toste, *Chem. Sci.*, 2015, **6**, 1194.
15 W.-J. Yoo and S. Kobayashi, *Green Chem.*, 2013, **15**, 1844.
16 J. Xuan, T.-T. Zeng, J.-R. Chen, L.-Q. Lu and W.-J. Xiao, *Chem. – Eur. J.*, 2015, **21**, 4962.
17 D. A. Nicewicz and T. M. Nguyen, *ACS Catal.*, 2014, **4**, 355.
18 This observation is in accordance with the results given by Kobayashi's group. See ref. 15.
19 A 6% reduction in the yield might be caused by molecular sieve powder blocking the light.
20 H. Yi, C. Bian, X. Hu, L. Niu and A. Lei, *Chem. Commun.*, 2015, **51**, 14046.
21 (a) M. Reckenthäler and A. G. Griesbeck, *Adv. Synth. Catal.*, 2013, **355**, 2727; (b) A. G. Griesbeck, J. Lex, K. M. Saygin and J. Steinwascher, *Chem. Commun.*, 2000, 2205.

A visible-light-induced oxidative phosphinylation of arylacetylenes catalyzed by an inexpensive organic dye was demonstrated to be effective under mild conditions.