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Article

Bisphosphonium salt: an effective photocatalyst for the intramolecular hydroalkoxylation of olefins

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ABSTRACT

A photocatalytic, intramolecular hydroalkoxylation of alkenes has been achieved by utilizing simple and readily available biphosphonium salts as an effective organic photocatalyst. The unique photocatalytic properties of biphosphonium salt enables facile oxidations of substituted alkenes to facilitate the streamline and regioselective synthesis of a series of saturated cyclic ethers from simple alkenes under mild conditions.

1. Introduction

Over the last decade, chemists have witnessed tremendous progress in the development of visible-light-induced photoredox catalysis that could enable a diverse of novel and challenging transformations under mild conditions [1–13]. Generally, most of the commonly employed photocatalysts are transition-metal complexes, represented by polypyridyl complexes of ruthenium and iridium, due to their unique photophysical and photochemical properties [1–6]. Despite these great achievements, concerns from associated with transition-metal contamination in pharmaceutical and material industries has driven the exploration of simple organic molecules as suitable replacements to transition metal-based photocatalysts. Compared to metal-based complexes, organic photocatalysts are typically more economical, easily prepared and structurally tunable, and less toxic and environmentally damaging. Therefore, the utilization of organic photocatalysts for visible light photocatalysis would merit the growing needs for green and sustainable development. Indeed, organic dyes, such as xanthenes, thiazines, benzophenones, and acridinium salts, have been widely explored as photocatalysts for a wide range of organic transformations as well as polymer synthesis [14–17]. However, some of these organic photocatalysts exhibit narrow redox window and tendency to photo bleaching, thus, to a certain extent, decrease the potential application of organic photoredox catalysis in chemical synthesis. Therefore, it is still highly in demand to identify new chromophores as a suitable and efficient complement for previously employed organic-based and transition-metal-based photocatalysts [18].

Saturated cyclic ethers are important structural scaffolds found in many biologically active natural products, pharmaceuticals and agrochemicals [19]. One of the most straightforward and attractive synthetic strategies for constructing these cyclic ether motifs is the catalytic intramolecular hydroalkoxylation of alkenes enabled by transition metals or Lewis acids, generally delivering Markovnikov-type addition products [20,21–33]. Recently, Nicewicz and coworkers reported a catalytic intramolecular *anti*-Markovnikov hydroalkoxylation of alkenes via visible light photoredox catalysis [34–36]. In this transformation, a crucial design for such *anti*-Markovnikov selectivity is harnessing the unique reactivity of alkene radical cations, generated via single electron oxidation of alkenes by a photoexcited, highly oxidative acridinium salt.

Our research groups focus on the development of novel and sustainable photocatalysts to enable the direct activation of organic molecules, with particular attention to these with high redox potentials. Recently, we have successfully identified simple cerium salts as effective photocatalysts for the direct activation of diverse alcohols into versatile alkoxy radical species under mild conditions [37–41]. During our pursuit for a more sustainable and practical alternative, we pleasingly found that biphosphonium salt, firstly prepared from 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) by the group of Anslyn [42], could function as an efficient

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photocatalyst for the SET oxidation of olefins, and thereby could promote the catalytic intramolecular hydrofunctionalization of alkenols (Fig. 1). Herein, we disclosed this visible light-induced intramolecular hydroalkoxylation of alkenols by utilizing biphosphonium salt as a photocatalyst. We believe this new biphosphonium salt-based organic photoredox catalysis system would provide an alternative to Nicewicz's acridinium protocol, and more importantly, would shed some light on the potential application of biphosphonium salt as an efficient photocatalyst scaffold in organic synthesis.

2. Experimental

Commercial reagents were purchased from Aldrich, TCI, Energy Chemical and J&K chemical, and were used as received. All reactions were carried out in screw cap reaction tube under an atmosphere of argon unless otherwise noted. Chromatographic purification of products was accomplished by flash chromatography using silica gel. Thin-layer chromatography (TLC) was performed on Silicycle 250 mm silica gel F-254 plates. ^{1}H, ^{19}F NMR, and ^{13}C NMR spectra were recorded on Bruker 400 (400, 376, and 100 MHz) and Bruker 600 (600, 564, and 150 MHz), and are internally referenced to residual solvent signals (for $CDCl_3$, δ 7.26 and 77.0 ppm). Data for ^{1}H NMR and ^{19}F NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), integration, coupling constant (Hz). ^{13}C spectra were reported as chemical shifts in ppm and multiplicity where appropriate. High resolution mass spectra were obtained at ShanghaiTech mass spectrometry facilities. All alkenes were used from commercial suppliers or prepared according to literature procedures (Supporting Information online).

General procedure for biphosphonium salt-catalyzed intramolecular hydroalkoxylation of alkenols: A 8-mL vial was charged with alkene substrate (1.0 equiv.), 1,2-bis(2,4,6-triisopropylphenyl) disulfane (0.2 equiv.) and bisphosphonium salt **PC-1** (0.02 equiv.) in CH_3CN (0.1 mol/L). The vial was sealed with a polytertrafluoroethylene-lined cap, the reaction mixture was degassed by Argon sparging for 10 min, then irradiated with 400 nm LED (photon flux, 10 μ Einstein). The reaction was stirred under irradiation at ambient temperature. The reaction mixture was evaporated in vacuo, the residue was purified by flash chromatography to afford the product.

3. Results and discussion

Inspired by Koshevoy's recent work [43], which disclosed the optical behaviors of biphosphonium salt (**PC-1**), we began to evaluate the possibility of employing biphosphonium salt as new photoredox catalyst scafold. Irradiation the MeCN solution of alkene **1** with 400 nm LED for 1 h, in the presence of catalytic amounts of biphosphonium salt (**PC-1**) as photocatalyst and bis(2,4,6-triisopropylphenyl) disulfide $(TRIPS)_2$ as a HAT catalyst, led to the formation of the desired cyclic ether product **2** in 85% yield as a single regioisomer (Table 1, entry 1). No 6-*endo* cyclization product was observed in this case. As expected, the structure of HAT cocatalyst plays a crucial role to the reaction efficiency (entries 2–5). Only thiophenols and aryl disulfides could function as effective redox-active hydrogen atom donors, and $(TRIPS)_2$ is optimal (entries 1–3). Use of other hydrogen atom donors, such as hantzsch ester and triphenylsilane, resulted in the observation of trace amounts of cyclic ethers (entries 4, 5). No observation of the desired product in the absence of $(TRIPS)_2$ (entry 6). Furthermore, screening of solvents indicated that CH_3CN was the optimal reaction medium for this photocatalytic intramolecular cyclization (entries 7–12). Moreover, changing the light source from 400 nm LED to 365 nm LED or 90 W blue LED significantly decreased the reaction efficiency (entries 13, 14). This phenomenon was consistent to the optical absorption spectrum of biphosphonium salt shown in Fig. 2a. Finally, control experiments confirmed the photocatalytic nature of biphosphonium salt **PC-1** in this reaction, as no product is detected in the absence of photocatalyst or light (entries 15, 16).

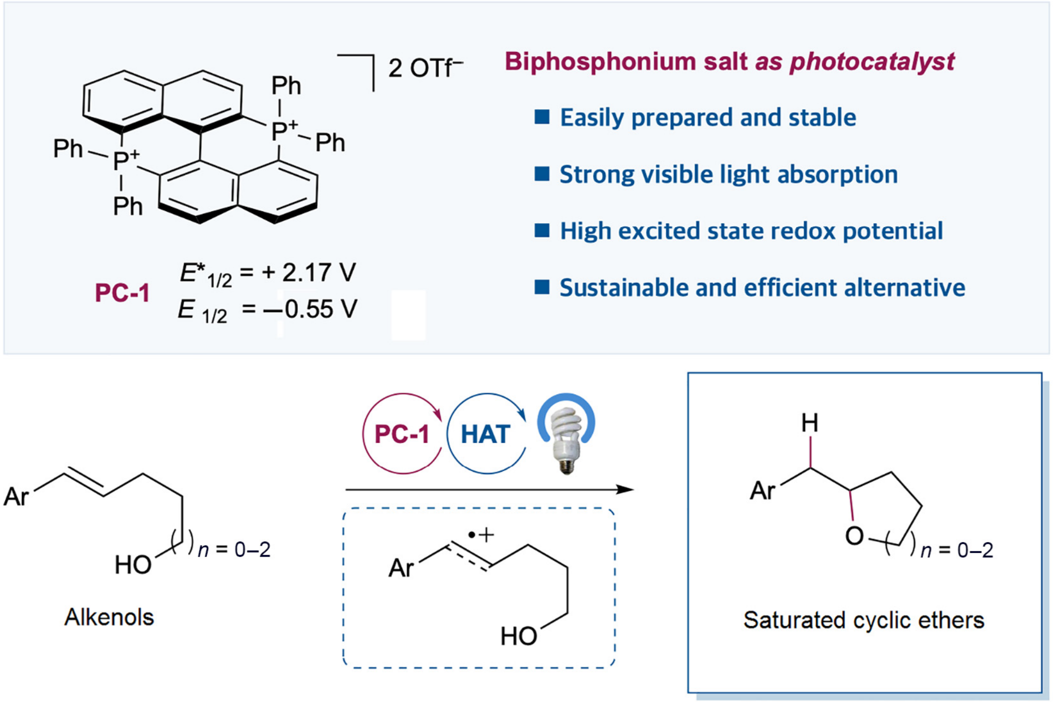
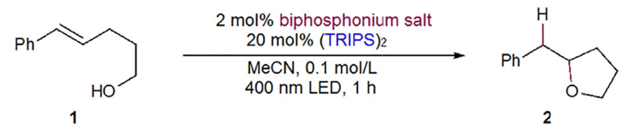
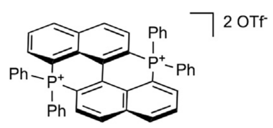


Fig. 1. (Color online) Biphosphonium salt as new photocatalyst for the intramolecular hydroalkoxylation of alkenols.

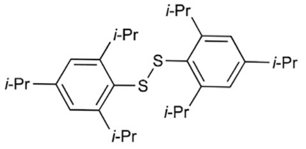
Table 1
Optimization of reaction conditions.[a]



Entry	Variations from the “standard” conditions	Yield (%)
1	None	85
2	$(PhS)_2$ instead of $(TRIPS)_2$	59
3	TRIPSH instead of $(TRIPS)_2$	42
4	Hantzsch ester instead of $(TRIPS)_2$	8
5	Ph_3SiH instead of $(TRIPS)_2$	1
6	No $(TRIPS)_2$	0
7	DCE instead of MeCN	72
8	DCM instead of MeCN	64
9	Acetone instead of MeCN	61
10	EA instead of MeCN	32
11	DMSO instead of MeCN	40
12	DMF instead of MeCN	9
13	90 W blue LED	60
14	365 nm LED	66
15	No **PC-1**	0
16	Dark	0



Biphosphonium salt, **PC-1**



$(TRIPS)_2$

[a] Reaction conditions: alkene (0.4 mmol), biphosphonium salt (2 mol%), $(TRIPS)_2$ (20 mol%), CH_3CN (0.1 mol/L), 400 nm LED. Yield was determined by GC analysis with an internal standard.

To the best of our knowledge, this represents the first example of visible light photoredox catalysis with biphosphonium salt as organic redox catalyst. To elucidate the catalytic properties of biphosphonium salt and gain some insight into the reaction mechanism, we performed a series of preliminary studies. First, the optical absorption spectrum of this biphosphonium salt **PC-1** dissolved in CH_3CN indicated an intense absorption around 400 nm, confirming its ability to absorb in the blue-light region (Fig. 2a). We also successfully recorded the emission spectrum of **PC-1** upon excitations at 331, 396, and 413 nm, demonstrating a maximum emission at 456 nm (Fig. 2b). Through time-resolved emission intensity decay studies (collected at 456 nm upon 360 nm excitation), the life time of the excited biphosphonium catalyst was determined to be 0.55 ns (Fig. 2c). Next, we measured the redox potentials of biphosphonium salt **PC-1** via cyclic voltammetry. We found that the reduced state of **PC-1** exhibited a moderate reductive capability ($E_{1/2} = -0.55$ V vs. SCE in CH_3CN) (Fig. 2d), and further estimated the excited state energy of **PC-1** ($E_{0,0} = 2.72$ eV) selecting the energy at the fluorescence maximum, thusly the reduction potential of the photoexcited state of **PC-1** can be estimated via the Rehm-Weller formalism ($E_{1/2}{}^{*} = +2.17$ V vs. SCE in CH_3CN).

On the basis of these preliminary results as well as previous work [34–36], we proposed a possible mechanistic pathway for this catalytic intramolecular hydroalkoxylation of alkenes (Fig. 3). Irradiation of **PC-1** with 400 nm LED would generate a photoexcited state of **PC-1*** **I**. The strongly oxidizing **PC-1*** ($E_{1/2}{}^{*} = +2.17$ V vs. SCE in CH_3CN) would be capable to oxidize alkene **1** ($E_{p/2} = +1.86$ V vs. SCE)[35] to afford the corresponding radical cation **III**, which could be trapped by the pendant hydroxyl group to give the radical species **IV**. Subsequent hydrogen atom transfer between radical **IV** and thiol **VIII** would furnish the protonated product **V** as well as thiyl radical **VI**. At this stage, a SET event between the reducing state of **PC-1** **II** ($E_{1/2} = -0.55$ V vs. SCE) and thiyl radical **VI** (PhS•, $E_{1/2} = +0.16$ V vs. SCE) [44] would produce

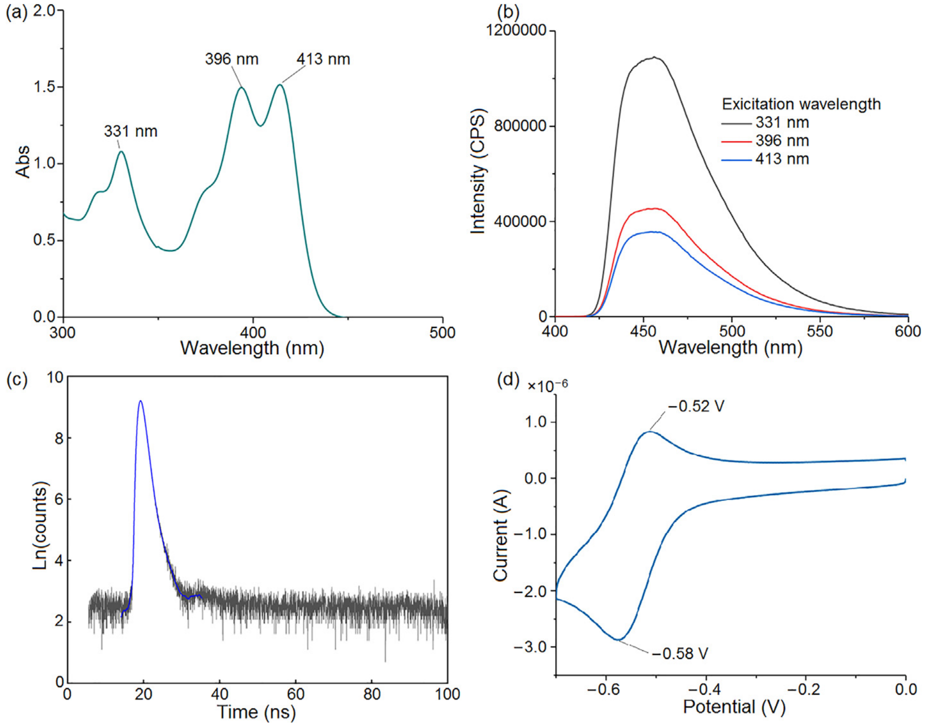


Fig. 2. (Color online) Photophysical properties of biphosphonium salt **PC-1**. (a) UV–vis absorption spectrum of **PC-1**; (b) emission spectrum of **PC-1**; (c) time-resolved emission intensity decay of **PC-1**; (d) cyclic voltammogram of **PC-1**.

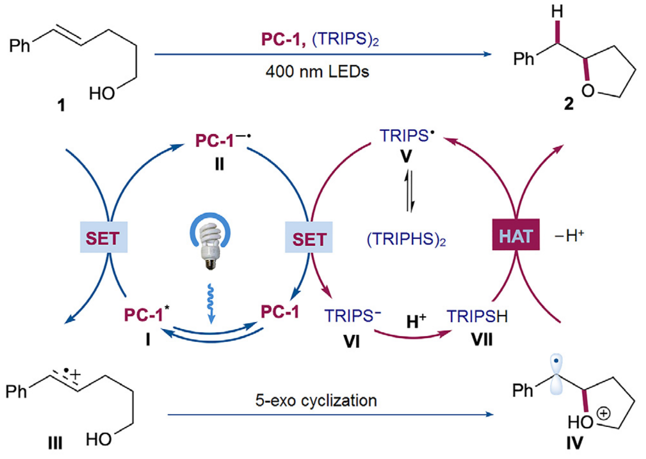
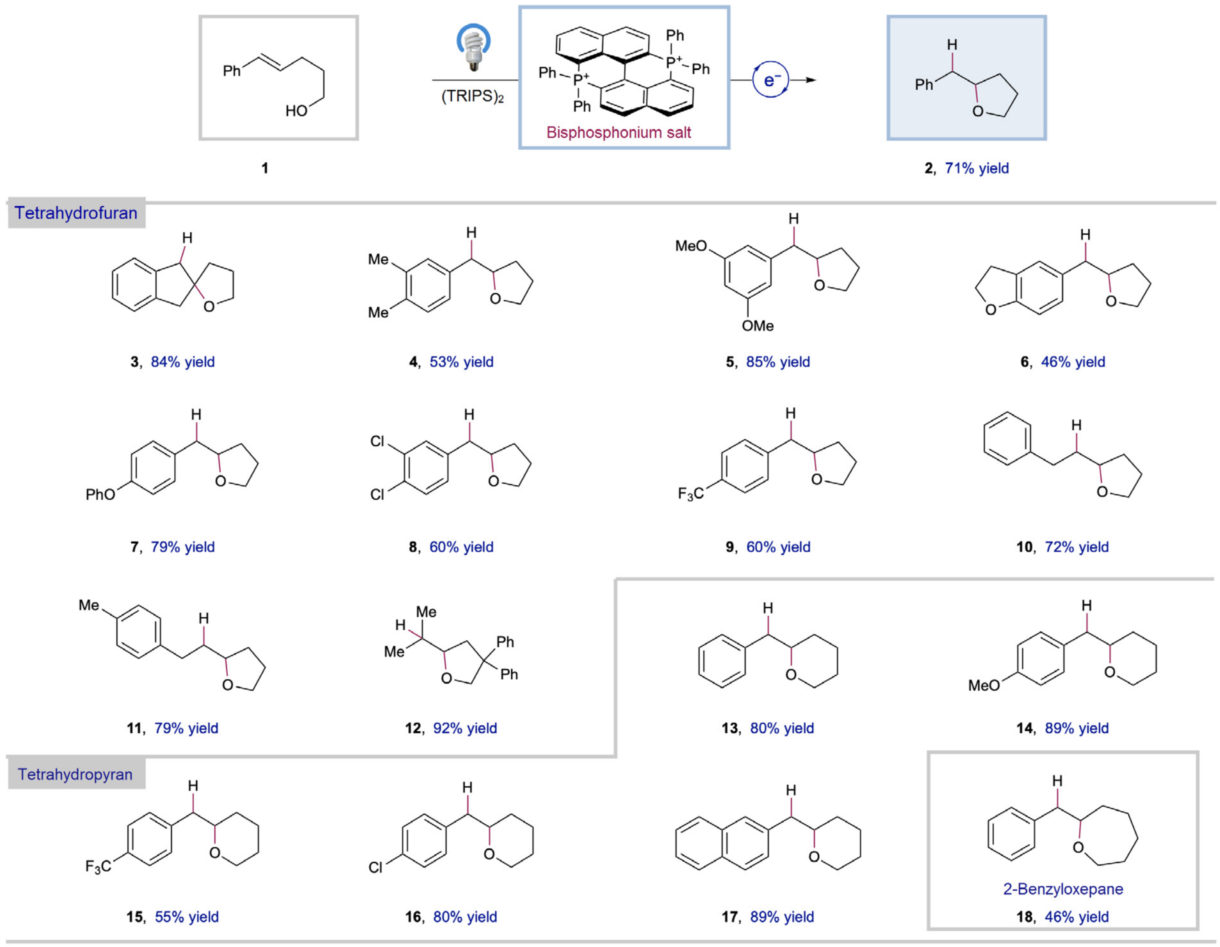


Fig. 3. (Color online) Proposed pathway.

thiolate **VII** and regenerate photocatalyst **PC-1** to close the photocatalytic cycle. Finally, proton transfer between the protonated product **V** and thiolate **VII** would furnish the desired final product **2** and regenerate the thiolphenol catalyst **VIII** to close the HAT cycle.

Next, we explored the generality of this biphosphonium salt-catalyzed intramolecular hydroalkoxylation of alkenes. As shown in Scheme 1, a variety of styrenes bearing electron-donating, -neutral, and -withdrawing groups underwent the desired 5-exo cyclization smoothly, affording the desired tetrahydrofuran products with moderate to good yields (products **2–9**, 46%–85% yields). Notably, indene was also a viable substrate for this photocatalytic system, forging the spirocyclic ether product in 84% yield (products **3**, 84% yield). Besides styrenes, unactivated alkenes that typically show higher reduction potentials also worked well under the optimal conditions, furnishing the corresponding 5-exo adducts with good efficiency (products **10–12**, 72%–92% yields). As expected, the cyclization efficiency could be enhanced by Thorpe-Ingold effect. For instance, 92% yield of the 5-exo cyclization product **12** was obtained in the case of an alkene containing two gem-diphenyl substituents (products **12**, 92% yield). Importantly, this biphosphonium salt-enabled photoredox cyclization protocol could be applied to construct larger ring systems. Under the mild conditions, electron-rich, -neutral, and -poor styrenes underwent the desired 6-exo cyclization with complete selectivity, furnishing a series of tetrahydropyrans with moderate to high yields (products **13–17**, 55%–89% yields). Pleasingly, this photocatalytic cyclization protocol could be applied to construct oxepane motifs from simple alkenes with synthetic useful yields, as exemplified by compound **18**, further demonstrating its synthetic applicability. It should be noted that this photocatalytic system demonstrates complete regioselectivity, and only anti-Markovnikov type adducts were observed in all cases (Scheme 1).



Scheme 1. (Color online) Alkene scope. Reaction conditions: alkene (0.4 mmol), biphosphonium salt (2 mol%), (TRIPS)$_2$ (20 mol%), CH_3CN (0.1 mol/L), 400 nm LED. Isolated yields.

4. Conclusion

In conclusion, we have developed an intramolecular hydroalkoxylation of alkenes by utilizing simple and readily available biphosphonium salts as an effective organic photoredox catalyst. This mild protocol enables a streamline and regioselective synthesis of a series of saturated cyclic ethers from simple alkenols. Due to the unique photocatalytic properties of biphosphonium salt, we believe this new catalyst scaffold would find potential application in the area of visible light photoredox catalysis.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgments

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Author contributions

Zhiwei Zuo and Lingling Chu conceived and designed the project, Zhiwei Zuo, Lingling Chu and Hao Cheng designed the experiments, Hao Cheng, Xin Wang, Lingling Chu, and Yilin Chen performed the experiments and analyzed the data, Zhiwei Zuo and Lingling Chu prepared the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scib.2019.08.014.

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