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# Photocatalytic Aldehyde C–H Bond Phosphonioethylation with Vinylphosphonium Bromide

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Supporting information for this article is given via a link at the end of the document.

**Abstract:** Photocatalytic C–H bond phosphonioethylation of aldehydes with vinylphosphonium bromide has been developed. Various  $\beta$ -phosphonioalkylketones are synthesized from readily available aldehydes under neutral conditions. Mechanistic studies suggest that C–H activation of aldehydes occurs through hydrogen-atom transfer by a bromine radical and that an alcoholic additive, which showed marked effects in increasing the efficiency of the reaction, is involved in the reaction as a proton source.

## Introduction

$\beta$ -Phosphonioalkylketones and aldehydes are versatile intermediates possessing two different functionalities, carbonyl and phosphonio groups, which can be utilized as a homologating agent<sup>[1]</sup> for the synthesis of various functionalized alkenes including natural products and pharmaceuticals.<sup>[2]</sup>  $\beta$ -Phosphonioalkylketones are conventionally synthesized through conjugate addition of tertiary phosphines to  $\alpha,\beta$ -unsaturated ketones in the presence of acids such as hydrogen bromide (Figure 1a).<sup>[3]</sup> Recent progress on photoinduced radical reactions has facilitated the synthesis of ketones from aldehydes and activated alkenes through addition of acyl radical intermediates.<sup>[4]</sup> For example, Wu and coworkers demonstrated that a photochemically generated bromine radical abstracts a hydrogen atom from an aldehyde to give an acyl radical, which reacts with an activated alkene to form a ketone.<sup>[5]</sup> However, there are no reported examples of the synthesis of  $\beta$ -phosphonioalkylketones starting from aldehydes. Photocatalytic Giese-type radical addition reactions have been rapidly developing in the last decade.<sup>[6]</sup> Various radical acceptors, activated alkenes, were so far examined in this field. Among them, Silvi demonstrated that vinylphosphonium salts worked as a radical acceptor to achieve conjunctive olefination between carboxylic acids and aldehydes.<sup>[7]</sup> Our group has also reported the photocatalytic anti-Markovnikov addition of the  $\alpha$ -C–H bond of alcohols to vinylphosphonium bromide.<sup>[8]</sup> In this reaction,  $\alpha$ -C–H activation of alcohols occurs through hydrogen

atom transfer by a bromine radical, which is photocatalytically generated from a vinylphosphonium bromide. Extending this strategy, we envisioned that  $\beta$ -phosphonioalkylketones could be synthesized in the reaction of aldehydes with vinylphosphonium bromide. Here, we report photocatalytic aldehyde C–H phosphonioethylation with vinylphosphonium bromide (Figure 1b). Various  $\beta$ -phosphonioalkylketones were synthesized from readily available aldehydes and vinylphosphonium bromide under neutral reaction conditions.

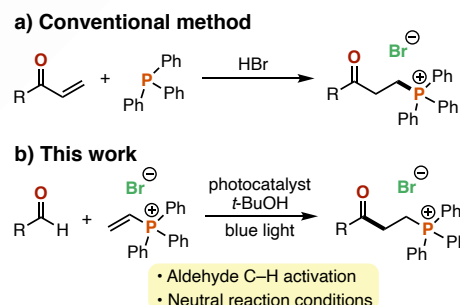


Figure 1. Synthesis of  $\beta$ -phosphonioalkylketones.

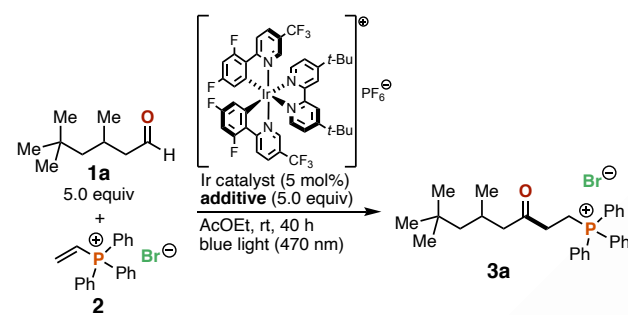
## Results and Discussion

### Effect of Additives

Initially, we performed the reaction of aldehyde **1a** with vinyltriphenylphosphonium bromide (**2**) under reaction conditions identical to those in our previous report. A solution of aldehyde **1a** (0.50 mmol, 5.0 equiv), vinylphosphonium bromide **2** (0.10 mmol), and [Ir(dFCF<sub>3</sub>ppy)<sub>2</sub>dtbbpy]PF<sub>6</sub> (Ir catalyst, 0.005 mmol, 5 mol%) in ethyl acetate (AcOEt, 1 mL) was irradiated with blue light (470 nm) at ambient temperature for 40 h. An NMR analysis of the crude mixture showed that  $\beta$ -phosphonioalkylketone **3a** was obtained in 25% yield with 67% recovery of the starting phosphonium salt (**2**) (Table 1, entry 1). Since the solubility of **2**

in AcOEt was low, several additives that can dissolve **2** were examined to improve the reaction efficiency. Addition of acetonitrile (CH<sub>3</sub>CN) or dichloromethane (CH<sub>2</sub>Cl<sub>2</sub>) resulted in a slight increase in the product yield (entries 2 and 3). Protic additives such as benzoic acid and hexafluoro-2-propanol (HFIP) were found to be more effective, affording **3a** in 76% and 80% yields, respectively (entries 4 and 5). Finally, a quantitative yield of **3a** was obtained by using *tert*-butyl alcohol (*t*-BuOH) as an additive. The product was isolated by chromatographic purification in 95% yield (entry 6). Reducing the catalyst loading or the amount of aldehyde resulted in lower conversion of **2**, making it difficult to isolate the product (**3a**) from a mixture of **3a** and **2** (see the Supporting Information for details of the optimization study).

**Table 1.** Effect of additives<sup>[a]</sup>



| Entry | Additive                        | Yield of <b>3a</b> |
|-------|---------------------------------|--------------------|
| 1     | none                            | 25%                |
| 2     | CH <sub>3</sub> CN              | 46%                |
| 3     | CH <sub>2</sub> Cl <sub>2</sub> | 43%                |
| 4     | PhCO <sub>2</sub> H             | 76%                |
| 5     | HFIP                            | 80%                |
| 6     | <i>t</i> -BuOH                  | 92% <sup>[b]</sup> |

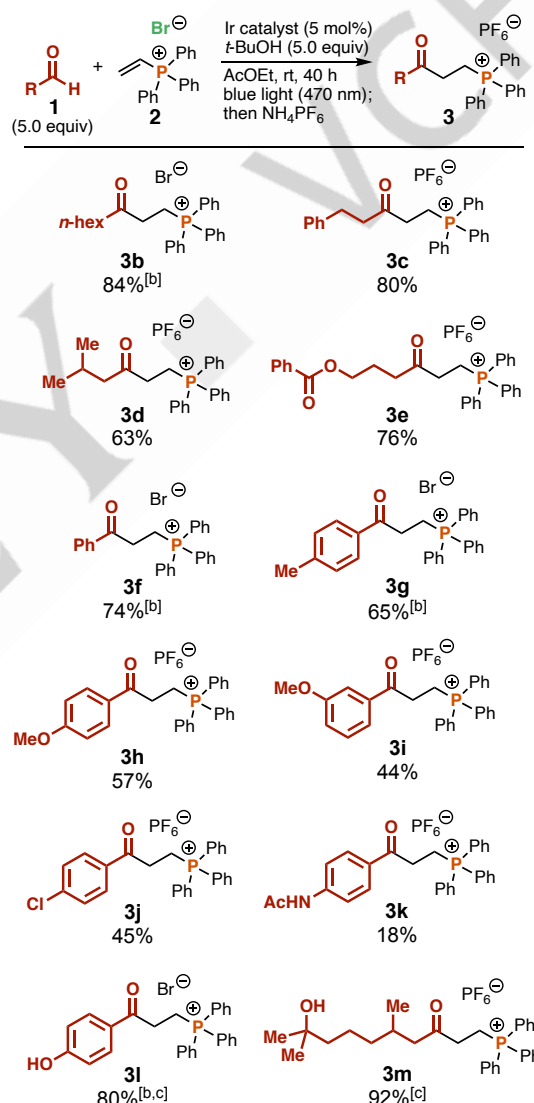
[a] **1a** (0.50 mmol, 5.0 equiv), **2** (0.10 mmol), additive (0.50 mmol, 5.0 equiv), AcOEt (1 mL), blue LEDs (470 nm), ambient temperature, 40 h. Yields determined by <sup>1</sup>H NMR analysis using triphenylmethane as an internal standard. [b] Isolated yield.

### Substrate Scope

The phosphonioethylation reaction was applied to various aldehydes (Table 2). Aliphatic aldehydes such as heptanal, 3-phenylpropanal, and 3-methylbutanal afforded the corresponding phosphonium salts in good yields (**3b–3d**). The reaction was applicable to benzyloxy-substituted alkylaldehyde **3e**. Aromatic aldehydes also participated in the present reaction. Functional groups on the aromatic ring, such as methyl, methoxy, chloro, and acetyl amino groups, were all tolerated under the reaction conditions to obtain the corresponding phosphonium

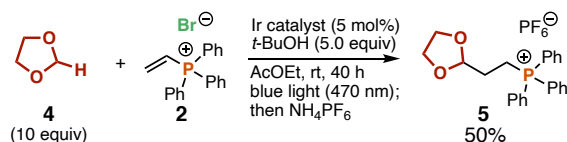
salts (**3g–3k**) in yields ranging from 18% to 57%. Notably, aldehydes possessing a hydroxy group, hydroxycitronellal and 4-hydroxybenzaldehyde, gave the desired products (**3l** and **3m**) in high yields without the addition of *t*-BuOH. On the other hand, sterically bulky aliphatic aldehydes and electron-deficient aromatic aldehydes failed to give  $\beta$ -phosphonioalkylketones (see the Supporting Information for details). Most of the produced bromide salts were difficult to purify due to high polarity, and thus, they were isolated as hexafluorophosphate salts after anion exchange.

**Table 2.** Substrate scope<sup>[a]</sup>



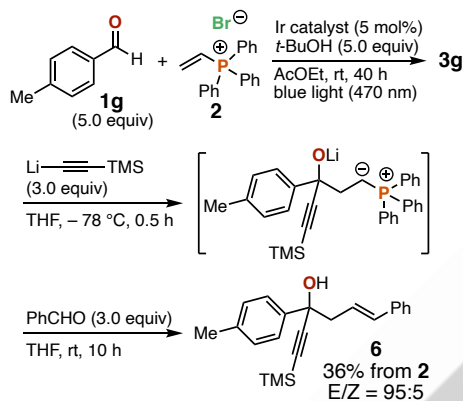
[a] Reaction conditions: aldehyde (0.50 mmol, 5.0 equiv), **2** (0.10 mmol), *t*-BuOH (0.50 mmol, 5.0 equiv), Ir catalyst (0.005 mmol, 5 mol%), AcOEt (1 mL), rt, 40 h, blue LEDs (470 nm). [b] Isolated as a bromide salt without salt exchange. [c] In the absence of *t*-BuOH.

The present method was applicable to C–H phosphonioethylation of 1,3-dioxolane (**4**).<sup>[9]</sup> The reaction of **4** and **2** afforded phosphonium salt **5**, which is a protected form of  $\beta$ -phosphonioalkylaldehyde, in 50% yield.



**Scheme 1.** Phosphonioethylation of 1,3-dioxolane (**4**)

Next, we performed a one-pot bifunctionalization of the produced  $\beta$ -phosphonioalkylketone. The crude mixture of **3g** obtained in the reaction of **1g** and **2** was treated with an excess amount of lithium (trimethylsilyl)acetylide. One equivalent of acetylide added to the carbonyl group and the remained acetylide worked as a base to generate a phosphorus ylide. Finally, addition of benzaldehyde to the reaction mixture afforded 1,5-enyne **6** with high *E* selectivity (Scheme 2).<sup>[10]</sup>

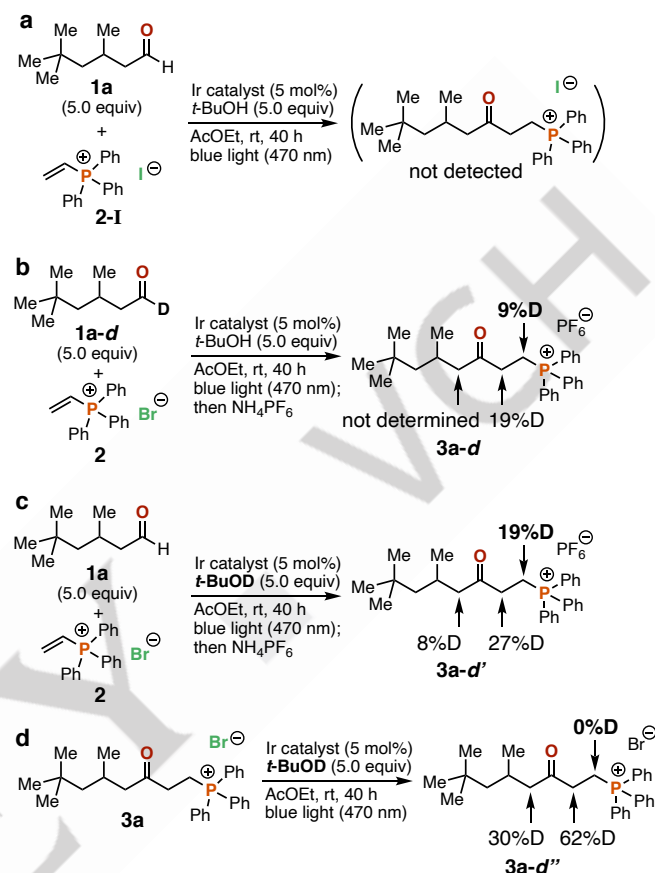


**Scheme 2.** Derivatization of  $\beta$ -phosphonioalkylketone **3g**

## Mechanistic Experiments

The following experiments gave mechanistic insights into the aldehyde C–H phosphonioethylation. When the reaction was carried out with vinylphosphonium iodide **2-I** instead of phosphonium bromide **2**, no reaction occurred (Scheme 3a). This suggests the involvement of hydrogen atom transfer (HAT) mediated by a bromine radical in the reaction mechanism as in the case of our previous report.<sup>[8]</sup> Next, we performed the reaction with **2** using an aldehyde deuterated at the carbonyl carbon (**1a-d**). The deuterium atom was transferred to the position  $\alpha$  to the phosphorus atom in product **3a-d** (Scheme 3b). The low deuterium/hydrogen ratio in **3a-d** indicated the existence of another hydrogen source in the reaction system. When the reaction of **1a** and **2** was conducted in the presence of monodeuterated *tert*-butyl alcohol (*t*-BuOD), the product (**3a-d'**) possessed deuterium atoms at the  $\alpha$  position of the phosphorus atom and at the  $\alpha$  positions of the carbonyl group (Scheme 3c). When the same deuteration reaction was carried out with **3a** instead of a mixture of **1a** and **2**, deuterium atoms were introduced only at the  $\alpha$  positions of the carbonyl group, indicating the occurrence of keto-enol tautomerization under the

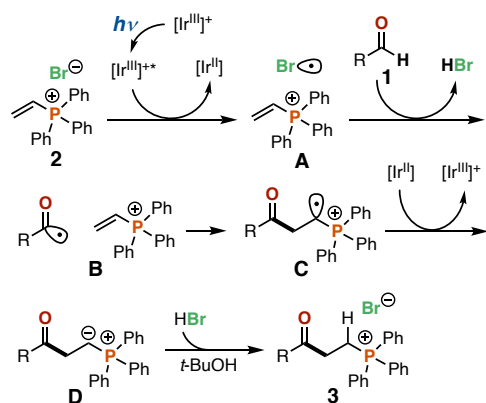
reaction conditions (Scheme 3d).<sup>[11]</sup> Deuteration at the position  $\alpha$  to the phosphorus atom in the reaction of **1a** and **2** in the presence of *t*-BuOD (Scheme 3c) suggests that the reaction involves protonation of the P-adjacent carbon with *t*-BuOH.



**Scheme 3.** Mechanistic experiments

## Proposed Mechanism

Based on the above experimental results, we propose the reaction pathway depicted in Scheme 4. Initially, the photocatalyst ( $[\text{Ir}^{\text{III}}]^+$ ) is excited upon photoirradiation, and the excited state of catalyst ( $[\text{Ir}^{\text{III}}]^*$ ,  $E([\text{Ir}^{\text{III}}]^*/[\text{Ir}^{\text{III}}]) = +1.21 \text{ V vs SCE in } \text{CH}_3\text{CN}$ )<sup>[12]</sup> oxidizes the bromide anion of phosphonium salt **2** [ $E(\text{Br}^-/\text{Br}^\cdot) = +1.22 \text{ V vs SCE in acetone}$ ]<sup>[13]</sup> to bromine radical (**A**).<sup>[14,15]</sup> The bromine radical in **A** abstracts a hydrogen atom at the C–H bond of aldehyde **1** to generate acyl radical **B** and hydrogen bromide (HBr).<sup>[5]</sup> The addition of the acyl radical to the alkene terminal of the vinylphosphonium ion gives phosphonium-adjacent alkyl radical **C**.<sup>[16]</sup> Single-electron transfer to **C** from the reduced state of the photocatalyst ( $[\text{Ir}^{\text{II}}]$ ) forms the corresponding phosphorus ylide **D**, which is protonated by HBr, either directly or mediated by *t*-BuOH, to furnish  $\gamma$ -oxoalkylphosphonium bromide **3**.



**Scheme 4.** Proposed reaction pathway

## Conclusion

We developed photocatalytic phosphonioethylation of aldehyde C–H bonds with vinylphosphonium bromide. An alcoholic additive, *tert*-butyl alcohol, had a significant impact on increasing the product yield. Various  $\beta$ -phosphonioalkylketones were synthesized under neutral reaction conditions. Mechanistic studies suggested that C–H activation of aldehydes occurs through hydrogen atom transfer by a bromine radical and that *tert*-butyl alcohol is involved in the reaction as a proton source.

## Experimental Section

**Typical procedure for the photocatalytic reaction of 1a and 2.** To an oven-dried 4 mL vial equipped with a stirring bar, [Ir(dFCF<sub>3</sub>ppy)<sub>2</sub>dtbbpy]PF<sub>6</sub> (Ir catalyst, 5.6 mg, 0.005 mmol, 5.0 mol%) and triphenylvinylphosphonium bromide (2, 36.9 mg, 0.10 mmol) were added. The vial was purged with argon gas and was brought into a nitrogen-filled glove box. In the glove box, 3,5,5-trimethylhexanal (1a, 0.087 mL, 0.50 mmol, 5.0 equiv), anhydrous AcOEt (1.0 mL), and *t*-BuOH (0.048 mL, 0.50 mmol, 5.0 equiv) were added to the vial. The vial was capped and taken out from the glove box, and the suspension was stirred under photoirradiation (470 nm) at room temperature for 40 h. After irradiation, the reaction mixture was transferred to an oven-dried 30 mL flask, and the solvent was removed under reduced pressure. The crude mixture was purified by SiO<sub>2</sub> column chromatography (MeOH/CHCl<sub>3</sub> = 0:100 to 5:95) followed by reprecipitation (CH<sub>2</sub>Cl<sub>2</sub>/Et<sub>2</sub>O) to give 3a as light-yellow solids (47.0 mg, 0.092 mmol, 92% yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.85–7.77 (m, 9H), 7.73–7.68 (m, 6H), 4.06 (dt,  $J_{\text{H-P}}$  = 12.8 Hz,  $J$  = 5.5 Hz, 2H), 3.24–3.07 (m, 2H), 2.30 (dd,  $J$  = 17.4, 5.5 Hz, 1H), 2.22 (dd,  $J$  = 17.4, 7.8 Hz, 1H), 1.94–1.84 (m, 1H), 0.99–0.97 (m, 2H), 0.81 (s, 9H), 0.72 (d,  $J$  = 6.4 Hz, 3H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):  $\delta$  205.7 (d,  $J_{\text{C-P}}$  = 6 Hz), 135.0 (3C), 133.6 (d,  $J_{\text{C-P}}$  = 10 Hz, 6C), 130.4 (d,  $J_{\text{C-P}}$  = 12 Hz, 6C), 118.1 (d,  $J_{\text{C-P}}$  = 86 Hz, 3C), 51.7, 50.4, 35.7, 30.9, 29.8 (3C), 25.1, 22.3, 16.2 (d,  $J_{\text{C-P}}$  = 55 Hz); <sup>31</sup>P NMR (162 MHz, CDCl<sub>3</sub>):  $\delta$  26.5; HRMS (ESI)  $m/z$ : [M<sup>+</sup>] Calcd for C<sub>29</sub>H<sub>36</sub>OP<sup>+</sup> 431.2498, Found 431.2494, [M<sup>+</sup>] Calcd for

Br<sup>−</sup> 78.9189, Found 78.9190; IR (ATR): 2957, 2928, 2858, 1716, 1588, 1485, 1439, 1112, 997, 828, 741, 723, 689 cm<sup>−1</sup>.

## Supporting Information

The authors have cited additional references within the Supporting Information.

## Acknowledgements

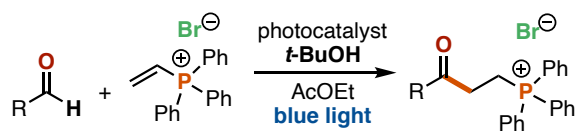
This work was supported by JSPS KAKENHI Grant Nos. JP21H04680 in Grant-in-Aid for Scientific Research (A) (MS), JP23K04728 in Grant-in-Aid for Scientific Research (C) (YM), JP22H05331 in Grant-in-Aid for Transformative Research Area (A) Digitalization-driven Transformative Organic Synthesis (Digi-TOS) (YM), and Astellas Foundation for Research on Metabolic Disorders (YM). The authors thank the Open Facility, Global Facility Center, Creative Research Institution for mass spectrometry measurements. The authors thank Dr. Keisuke Imaeda and Prof. Dr. Kosei Ueno (Hokkaido University) for fluorescence spectroscopic analysis.

**Keywords:** phosphonium salt • aldehyde • photoredox catalyst • hydrogen atom transfer • bromine radical

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## Entry for the Table of Contents



- Aldehyde C–H activation
- Neutral reaction conditions

Photocatalytic C–H bond phosphonioethylation of aldehydes with vinylphosphonium bromide has been developed. Addition of *tert*-butyl alcohol significantly increased the reaction efficiency. Various  $\beta$ -phosphonioalkylketones were synthesized from readily available aldehydes under neutral conditions. Mechanistic experiments suggest the role of *tert*-butyl alcohol as a proton source.