



## **Accepted Article**

**Title:** Visible-Light-Promoted Formation of C–C and C–P Bonds Derived from the Evolution of Bromoalkynes under Additive-Free Conditions: Synthesis of 1,1-Dibromo-1-en-3-ynes and Alkynylphosphine Oxides

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### Visible-Light-Promoted Formation of C–C and C–P Bonds Derived from the Evolution of Bromoalkynes under Additive-Free Conditions: Synthesis of 1,1-Dibromo-1-en-3-ynes and Alkynylphosphine Oxides

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Jummary of main observation and conclusion The controllable achievement of C–C and C–P bond formations is developed via visible-light-promoted bromoalkyne dimerization or its further transformation with secondary phosphine oxides. The 1,1-dibromo-1-en-3-ynes are formed when bromoalkyne is xposed to visible-light. While alkynylphosphine oxides are generated when bromoalkynes are mixed with secondary phosphine oxides.

#### **Background and Originality Content**

Finding a facile synthetic platform to construct chemical honds is an important and eternal challenge for chemists. In particular, the construction of the C–C bond is of undoubted importance in organic studies. Until now, innumerable reported \*ransition-metal catalyzed coupling synthetic strategies have been applied in C–C bond formation to form diverse organic molecules. lowever, here, we focus on the C–C coupling reaction of alkynes or their derivatives. Under conventional cognition, uta-1,3-diynes or 1,4-enynes were usually obtained via the lead-to-head coupling of alkynes or their derivatives.<sup>1</sup> Nevertheless, the head-to-tail coupling of alkynes or their erivatives remains challenging to synthesize conjugated 1,3-enynes, which are important structural units in natural products, biological molecular, organic composites and other materials.<sup>2</sup> Limited reports have realized the head-to-tail coupling ynes to produce conjugated 1,3-enynes due to the difficulties in regioselectivity.<sup>3</sup> For example, the [Pd]-catalyzed ead-to-tail coupling of terminal acetylenes is the main and effective synthetic strategy to synthesize 1,3-enynes;<sup>4</sup> in addition, the same synthetic target was achieved when the similar reaction ccurred in the presence of other transition-metal salts such as [Fe]-,<sup>5</sup> [Rh]-,<sup>6</sup> [Au]-catalyst<sup>7</sup> and actinide precatalysts<sup>8</sup> (Scheme 1a). Meanwhile, 1,3-enynes can be produced from the navailable complicated synthetic precursor under harsh conditions.<sup>9</sup> Nonetheless, the above developed dimerization reactions of terminal acetylenes cannot work without metal

A glance at the literature shows that haloacetylenes have een employed as an alternative precursor to achieve the head-to-tail coupling reaction. In 1993, Barluenga et al demonstrated that iodoalkynes can react with one another for

atalysts and complicated conditions.

prepared iodinated enynes in the presence of Ipy<sub>2</sub>BF<sub>4</sub> and HBF<sub>4</sub> at -80 °C (Scheme 1b).<sup>10</sup> Another example of the head-to-tail coupling of iodoalkynes was observed by Hashimi via gold catalysis (Scheme 1c).<sup>11</sup> Han's group achieved this coupling transformation through multiple complicated reaction steps (Scheme 1d).<sup>12</sup> Goroff and coworkers studied a different derivation of tetrabromobutatriene that could obtain brominated

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enynes via Suzuki coupling, but they only obtained 12% yield with 'w chemoselectivity.<sup>13</sup> According to the current development and increasing demands in green and sustainable chemistry, it is .Ill significant for chemists to find a direct and convenient synthetic approach to construct 1,3-enynes under mild, green and fc asible conditions.

In recent years, remarkable progress has been made in developing different visible-light-promoted transformations to produce complicated and functional organic molecular, which cannot be replaced by conventional methods in many cases.<sup>14</sup> Bi omoalkynes, containing the *sp* hybridization of the triple bond atom, are used as important building blocks in versatile



3	_	CH₃CN	< 5 <sup>c</sup>
4	blue LED (420–425 nm)	CH₃CN	34 <sup>c</sup>
5	blue LED (450–455 nm)	CH₃CN	42 <sup>c</sup>
6	red LED (610–650 nm)	CH₃CN	< 5 <sup>c</sup>
7	green LED (480–570 nm)	CH₃CN	< 5 <sup>c</sup>
8	yellow LED (570–610 nm)	CH₃CN	< 5 <sup>c</sup>
9	blue LED (450–455 nm)	DCE	40 <sup>c</sup>
10	blue LED (450–455 nm)	EtOAc	33 <sup>c</sup>
11	blue LED (450–455 nm)	acetone	33 <sup>c</sup>
12	blue LED (450–455 nm)	CHCl₃	22 <sup>c</sup>
13	blue LED (450–455 nm)	toluene	< 5 <sup>c</sup>
14	blue LED (450–455 nm)	THF	< 5 <sup>c</sup>
15	blue LED (450–455 nm)	EtOH	< 5 <sup>c</sup>
16	blue LED (450–455 nm)	DMF	< 5 <sup>c</sup>
17	blue LED (450–455 nm)	DMSO	< 5 <sup>c</sup>
18	blue LED (450–455 nm)	CH₃CN	61
19	blue LED (450–455 nm)	CH₃CN	60 <sup><i>f</i></sup>
20	blue LED (450–455 nm)	CH₃CN	55 <sup>g</sup>
21	blue LED (450–455 nm)	CH₃CN	52 <sup><i>h</i></sup>
22	blue LED (450–455 nm)	CH₃CN	49 <sup><i>i</i></sup>

<sup>*a*</sup> (Reaction conditions: **1a** (0.30 mmol), light source, solvent (2.0 mL), r.t., N<sub>2</sub> atmosphere, 48 h.) <sup>*b*</sup> (Isolated yield.) <sup>*c*</sup> (the mixture was stirred for 24 h.) <sup>*d*</sup> (5 W blue LED was used.) <sup>*e*</sup> (7 W blue LED was used.) <sup>*f*</sup> (The mixture was stirred for 60 h.) <sup>*g*</sup> (The mixture was stirred for 72 h.) <sup>*h*</sup> (**1a** in CH<sub>3</sub>CN with 0.3 mol/L.) <sup>*i*</sup>(**1a** in CH<sub>3</sub>CN with 0.075 mol/L.)

transformations under different conditions.<sup>15</sup> Recently, we designed some work related to photoredox chemistry;<sup>16</sup> interestingly, the photoreaction could occur without additives, in particular, bromoalkynes in the photoreaction can be used as

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energetic photoactive molecules to achieve deep functional transformations.<sup>16d, 16e</sup> We found a trace amount of head-to-tail coupling product

((4,4-dibromobut-3-en-1-yne-1,3-diyl)dibenzene) was detected in the study of the controllable reaction of bromoalkynes with alcohols.<sup>16e</sup> To our delight, the head-to-tail coupling product could be obtained with acceptable yield by adjusting the visible-light wavelength and other conditions. Although Chen *et a*l. reported this reaction during our research (Scheme 1e),<sup>17</sup> we retained the efficiency of the head-to-tail coupling via simply adjusting the eaction ambient atmosphere in the absence of photocalyst (Scheme 1f); meanwhile, it should be speculated that the initiation mode of this developed photo-coupling transformation is also different. Further studies show that alkynylphosphine oxides were formed when secondary phosphine oxides switched ff the head-to-tail coupling by trapping the alkynyl radical derived from bromoacetylenes under

Scheme 2 Visible-light-induced head-to-tail coupling of <sup>+</sup> romoacetylenes<sup>a,b</sup>



<sup>a</sup> (Reaction conditions: **1** (0.30 mmol), CH₃CN (2.0 mL), at room ₂mperature, under blue LED irradiation for 48 h in N₂.) <sup>b</sup> (Isolated yield.)

visible-light irradiation. As we all know, alkynylphosphine oxides structural unit found in bioactive and material molecules,<sup>18</sup> however, most of reported synthetic mothods require harsh or complicated conditions.<sup>19</sup> Herein, we report a visible-light-promoted bromoalkyne head-to-tail dimerization and its further transformation with secondary phosphine oxides, which provides a convenient route to controllably achieve the C–C and C–P bond formation under photocatalyst- and additive-free conditions.

#### **Results and Discussion**

We commenced our investigation by dissolving phenylethynyl bromide (1a) in CH<sub>3</sub>CN, and the mixture was illuminated by blue LED (420-470 nm) for 24 h. Gratifyingly, the photoreaction provided (4,4-dibromobut-3-en-1-yne-1,3-diyl)dibenzene (2a) in 19% yield, and no better yield was observed by changing power of the light source (Table 1, entries 1 vs 2). Only a trace amount of 2a was observed when the light source was removed (Table 1, entry 3). The yield of 2a was improved to 34% and 42% when the wavelength of the blue LED was switched to 420-425 nm and 450-455 nm, respectively (Table 1, entries 4 and 5). When the coupling reaction was exposed to other light sources, such as red, green, or yellow LED light source, the reaction could not be effectively triggered (Table 1, entries 6–8). Unsatisfactory yields (22-40%) of desired product 2a were obtained when DCE, EtOAc, acetone and CHCl<sub>3</sub> were used as the solvent (Table 1, entries 9-12). Other solvents such as toluene, THF, EtOH, DMF, and DMSO were tested, worse results were obtained (Table 1, entries 13–17). The yield of 2a was improved to 61% with prolonged reaction time for 48 h (Table 1, entries 18 vs 19 and 20). When we further changed the concentration of **1a** in CH<sub>3</sub>CN, there was no

Scheme 3 Control experiments



obvious effect on the yield of 2a (Table 1, entries 21 and 22).

According to the results of the explored reaction conditions, the optimal reaction conditions were: **1a** (0.3 mmol) dissolved in

CH<sub>3</sub>CN; the mixture was irradiated under blue LED (450–455 nm) light for 48 h at room temperature in N<sub>2</sub> (Table 1, entry 18). A wide range of bromoacetylenes were employed to test the efficiency of the reaction under the optimized conditions, and the detailed results are listed in Scheme 2. Overall, substrates with electron-rich groups showed comparable reactivity to the electron-poor groups. For example, when the MeO, Me, Et, Pr, Bu or <sup>t</sup>Bu groups was at the *para*-position of the phenyl ring in bromoalkynes, the corresponding products (**2b–2g**) were afforded in 40–60% yields. Bromoalkynes **1** with electron-poor groups such as F, Cl, Br and CF<sub>3</sub> groups, also resulted in modest yields (34–58%) of the corresponding *gem*-dibromonated conjugated enynes products (**2h–2k**). The reactions of substrates **1** with a substituted

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group, including MeO, Me, F or Cl on the *meta*-position of the phenyl rings, generated the desired products (**2l–2o**) in 39–48% yields. Further investigation indicated that 2-substituted aromatic bromoalkynes, e.g., 1-(bromoethynyl)-2-chlorobenzene (**1p**) and 1-(bromoethynyl)-2-bromobenzene (**1q**), were also suitable for the coupling reactions and showed a slight steric hindrance effect (**2p** vs **2i**; **2q** vs **2j**). Meanwhile, heteroaromatic bromoalkyne **1r** was also converted to the desired product **2r**, although the yield was lower. It should be noted that the modest yields of the head-to-tail coupling in Scheme 2 were due to the incomplete c nversion of starting materials, and no other obvious byproduct was observed.

To explore the head-to-tail coupling pathway, some control experiments were performed, as shown in Scheme 3. The r action stopped when it was exposed to conventional heat sources or in the absence of visible light (Scheme 3a), which indirectly implied that the reaction cannot occur without visible-light irradiation. Furthermore, by quenching the reaction with radical scavengers such as TEMPO, only a trace amount of me desired product 2a was observed, which shown that the current transformation might be accomplished via a radical pathway. But we did not observe TEMPO could trap the any radical intermediate. Considering the results of control experiments and previous correlated reports, 16d, 16e, 20 the coupling action is presumably initiated via the homolytic cleavage of bromoalkynes. Alkynyl and bromine radical are generated during the homolytic transformation and perform the unfinished coupling process. According to the above speculation, we attempted to find suitable substrates to couple with radicals derived from bromoacetylenes, which might trigger another o oss-coupling reaction and interrupt the head-to-tail coupling of b omoacetylenes. Here, secondary phosphine oxides realized this assumption, and another coupling product (alkynylphosphine oxide) was observed.<sup>21</sup>

Subsequently, the coupling of bromoalkynes with secondary phosphine oxides was studied for the synthesis of ukynylphosphine oxides under visible-light irradiation in the absence of additive. The optimized conditions were determined by exploring various conditions (details are shown in the ESI). The obvious change in C–P bond formation was the use of CH<sub>2</sub>Cl<sub>2</sub> as a solvent by screening of different solvents (e.g. CH<sub>3</sub>CN, DCE,

**Scheme 4** Visible-light-promoted coupling of bromoalkynes with secondary phosphine oxides <sup>*a,b*</sup>



<sup>*a*</sup> [1 (0.20 mmol), **3** (0.60 mmol), CH<sub>2</sub>Cl<sub>2</sub> (6.0 mL) at room temperature under blue LED irradiation for 48 h in N<sub>2</sub>.] <sup>*b*</sup> (Isolated yields, and the yields in brackets were given based on recovered starting materials.)

toluene, acetone, EtOAc and EtOH), and the best reaction conditions: bromoalkynes 1 (0.20 mmol) and secondary phosphine oxides 3 (0.6 mmol) were mixed in CH<sub>2</sub>Cl<sub>2</sub> (6.0 mL), and the mixture was irradiated under blue LED (450–455 nm) for 48 h in N<sub>2</sub>. Different bromoalkynes and secondary phosphine oxides were investigated, and the results are shown in Scheme 4 (the isolated yield was calculated based on consumed 1). All bromoalkynes with different substituents on the phenyl ring smoothly reacted with diarylphosphine oxide to give the corresponding products (4a-4I) in 51-82% yield. For bromoalkynes, regardless of whether the electron-donation group or electron-withdrawing group was located at the para- or meta-position of the phenyl rings, the dehydrobromide coupling reaction was compatible to give the desired alkynyl(diaryl)phosphine oxides (4b-4i) in 60%-80% yields. When the substituent moved to the ortho-position of the phenyl rings in bromoalkynes, such as 1-(bromoethynyl)-2-chlorobenzene, product 4j was afforded in 51% yield, which shown the steric hindrance effect. Other diaryl-substituted phosphine substrates, e.g., di(4-methylphenyl)- and di(3,5-dimethylphenyl)-phosphine oxide, could also react with 1a and convert to the desired products 4k and 4l, respectively.

According to the above experimental results and related previous work, a plausible mechanism is outlined in Scheme 5. First, bromoalkyne **1a** was decomposed to form radical intermediate **A** with the concurrent release of a Br• radical in the presence of visible-light irradiation. Although this visible-light promoted homolytic cleavage procedure would be speculated by

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#### Scheme 5 Proposed mechanism



ome control experiments in previous correlated literature,<sup>16d,16e,17,20</sup> we cannot give a reasonable explain for the eal internal reason to promote occurrence of this homolytic procedure. Then, Br• combined with another **1a** to generate intermediate **B**, which coupled with intermediate **A** to produce he head-to-tail coupling product **2a**. It should be noted that product 2a also might be afforded from the addition reaction of Jinyl radical **B** to **1a** and concomitantly with concomitant formation of Br•. On the other hand, if diphenylphosphine oxide (3a) intervened in the coupling reaction, the binding of Br• to romoalkyne was inhibited; conversely, Br• was abstracted hydrogen from 3a to give diphenylphosphine oxide radical C, /hich reacted with intermediate A to afford phosphonoalkyne product 4a. Meanwhile, it should be noted that 4a also might be formed via the addition process of **C** to **1a** However, we cannot cetermine which is the main pathway for formation of 1,1-dibromo-1-en-3-ynes and alkynylphosphine oxides products.

#### Conclusions

In summary, we have developed a practical and convenient synthetic platform for the head-to-tail coupling of bromoalkynes in the presence of visible-light irradiation without any additive, and a series of *gem*-dibromonated conjugated enyne products is obtained in modest yields with good group tolerance. Notably, according to the reasonable logical assumption, this head-to-tail coupling was successfully switched to a cross-coupling reaction, and different alkynylphosphine oxides were produced via combinations of bromoalkynes with secondary phosphine oxides under similar reaction environments. Further studies of the visible-light-driven bromoalkyne transformations are in progress in our laboratory.

#### Experimental

General procedure for the synthesis of 1,1-dibromo-1-en-3-ynes **2**: bromoalkynes **1** (0.3 mmol) was issolved in acetonitrile (2.0 mL) under nitrogen atmosphere. The mixture was stirred under the blue LED (450-455 nm) irradiation for 48 h. The residue was then purified by column chromatography on silica gel (petroleum ether) to give the pure product **2**.

General procedure for the synthesis of alkynylphosphine oxides **4**: To a solution of diarylphosphine oxide **3** (0.6 mmol) in 6

mL of dichloromethane was added bromoalkynes **1** (0.2 mmol). The mixture was stirred in nitrogen atmosphere under the blue LED (450-455 nm) light source for 48 h. The residue was then purified by column chromatography on silica gel (petroleum ether/EtOAc = 1:1, v/v) to give the pure product 4.

#### **Supporting Information**

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2018xxxxx.

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mild conditions simple operation good regioselectivity

Visible-light-promoted synthesis of 1,1-dibromo-1-en-3-ynes and alkynylphosphine oxides via controllable formation of C–C and C–P bonds under photocatalyst-free conditions.

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