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# Redox-Neutral Photochemical Heck-Type Arylation of Vinylphenols Activated by Visible Light

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Disclosed herein is a photochemical Heck-type arylation of vinylphenols with non-activated aryl and heteroaryl halides under visible light irradiation. Preliminary mechanistic studies suggested that the colored vinylphenolate anions acted as a strong reducing photoactivator to directly activate (hetero)aryl halides without the requirement of any sacrificial reductants. The photochemically generated aryl radicals coupled with another molecule of vinylphenol to afford the Heck-type arylation product in regiospecific and stereoselective manner. The developed photochemical arylation protocol showed exceptionally functional group tolerance and was successfully applied in the challenging late-stage modification of natural products without any protecting-deprotecting procedures.

### Introduction

Introducing aryl- and heteroaryl units into molecular scaffolds is one of the fundamental chemical transformation in the syntheses of natural products, pharmaceuticals, or functional materials.<sup>1</sup> Over the past decades, transition-metalmediated arylation reactions have been well established, although some problems are still associated with these methods (i.e. expensive transition metal catalysts, specific and air-sensitive ligands, and elevated temperatures).<sup>2</sup> New cheap, efficient, and environmentally safe methodologies to realize the arylation are always of great interest. In recent years, visiblelight-induced radical arylation methods have been developed as attractive alternatives under mild conditions.<sup>3</sup> However, various photo-redox processes for arylation reactions required the use of electron-poor aryl diazonium salts<sup>4</sup> or diaryliodonium salts<sup>5</sup> as radical precursors (Scheme 1a). The reductive cleavage of non-activated (hetero)aryl halides, which are the most readily available and the cheapest arylation reagents, is limited by the redox properties of typical photocatalysts and the energy of the visible photon due to high negative reduction potentials of (hetero)aryl halides.<sup>6</sup>

In this context, development of powerful reducing photoreductants is an important synthetic goal. As depicted in Scheme 1b, recent examples of successful activations of (hetero)aryl halides with visible light are involved in three mechanistic scenarios: (i) direct single electron transfer (SET) from strongly reducing iridium,<sup>6a, 7</sup> copper,<sup>8</sup> N- phenylphenothiazine (PTH),<sup>9</sup> or 9-anthrolate anion<sup>10</sup> photocatalysts; (ii) indirect two-photon processes with organic dyes, such as perylene bisimides (PDIs),<sup>6b</sup> rhodamine 6G (Rh-6G),<sup>11</sup> 1,8-dihydroxyanthraquinone (Aq-OH),<sup>12</sup> and 9,10dicyanoanthracene (DCA)<sup>13</sup> by consecutive photo-induced SET cascades or with butane-2,3-dione (BD, sensitizer) and 2,5-diphenyloxazole (PPO, annihilator) by triplet-triplet



Scheme 1. a, Typical aryl radical precursors in visible-light-mediated arylation reactions. b, Reported strategies of visible-light-induced aryl halide activation. c, Redox-neutral photochemical Heck-type arylation of vinylphenols with (hetero)aryl halides.

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annihilation;<sup>14</sup> (iii) two-center photo-redox catalysis in which  $Ru(bpy)_{3}Cl_{2}$  absorbs the visible light and transfers the energy to pyrene that enables the redox reactions.<sup>15</sup> Although these photo-catalytic methods are highly innovative, most of them required a high excess of sacrificial reductants such as tertiary amines, sodium formate, or Hantzsch ester (HEH), resulting a fast competing hydrogen atom abstraction by the reactive aryl radicals to give undesired side products. Consequently, the reactivity of the resulting aryl radical has been confined to the hydrodehalogenation, 6, 7d, 12, 14 C-H arylation of electron-rich heteroarenes, 6b, 10-13, 15 and hydroarylation of alkenes. 7a-c, 8-9 However, the redox-neutral photochemical Heck-type arylation of alkenes under visible light is still a challenge and the only known example was reported by Chu and co-workers for the pyridylation of alkenes.<sup>16</sup> Evidently, development of new powerful photo-reductants that operate using mild visible light and do not require sacrificial reductants are highly warranted to alleviate side reactions and expand the synthetic applicability of aryl radicals from (hetero)aryl halides. Phenolate anions have been used as an attractive model system for photoinduced electron ejection mechanism study,<sup>17</sup> nevertheless, the photochemical reactivities of excited phenolate anions have received little attention. In 2015, Melchiorre and co-workers reported a redox-neutral photochemical strategy for the direct aromatic perfluoroalkylation of phenols.<sup>18</sup> In this reaction, excited phenolate anions directly acted as photoreductants to activate the perfluoroalkyl iodides. Inspired by these studies, we questioned whether phenolate anions could be employed as photoreductants to activate (hetero)aryl halides under a similar mechanistic model. Herein, we demonstrated that the colored vinylphenolate anions, in situ generated by deprotonation of vinylphenols, reached an electronically excited state upon visible-light irradiation and then act as effective photoreductants for the reductive activation of non-activated (hetero)aryl halides (Scheme 1c). This photochemical reaction overcame the need of sacrificial reductants and afforded Hecktype arylation products in regiospecific and stereoselective manner under redox-neutral conditions.

### **Results and discussion**

### **Optimization of reaction conditions**

The vinylphenol is an essential motif in a wide range of biologically active natural products and pharmaceuticals that accomplish a series of important functions.<sup>19</sup> Our initial explorations focused on the methyl 4-hydroxycinnamate 2, a key chromophore of the photoactive yellow protein (PYP).<sup>19e,</sup> <sup>20</sup>After investigating a range of reaction parameters, we discovered irradiating that the mixture of 4'bromoacetophenone 1 and 2 in DMSO with an 18 W blue light emitting diode (LED) lamp at room temperature for 16 hours with  $Cs_2CO_3$  as the base, the Heck arylation product **3** was formed in 87% yield (Table 1, entry 1). The structure of the desired product **3** was unambiguously assigned by X-ray crystallography. Interestingly, this photochemical process exhibited a complete opposite regioselectivity compared with traditional palladium catalyzed Heck arylation reactions,<sup>21</sup> and afforded the tri-substituted alkenes in a stereoselective manner (E/Z > 19:1). Controlled reactions established that this reaction did not occur in dark even after heat to 80 °C, thus demonstrating the photochemical nature of the reaction

Table 1: The model reaction and the reaction parameters evaluated.	icle Online
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DOI: 10.1039/C9SC06184C blue LED Cs<sub>2</sub>CO<sub>3</sub> DMSO Ar, rt, 16h Change from standard conditions yield (%)<sup>b</sup> entrv 87 1 none 2 no light 0 3 no light and heat to 80 °C 0 4 23W CFL, instead of blue LED 56 5 30W white LED, instead of blue LED 50 0 6 no base 7 KHCO<sub>3</sub>, instead of Cs<sub>2</sub>CO<sub>3</sub> 53 8 Na<sub>2</sub>CO<sub>3</sub>, instead of Cs<sub>2</sub>CO<sub>3</sub> 40 9 K<sub>2</sub>CO<sub>3</sub>, instead of Cs<sub>2</sub>CO<sub>3</sub> 73 10 K<sub>3</sub>PO<sub>4</sub>, instead of Cs<sub>2</sub>CO<sub>3</sub> 43 11 DBU, instead of Cs<sub>2</sub>CO<sub>3</sub> 51 TMG, instead of Cs<sub>2</sub>CO<sub>3</sub> 54 12 Et<sub>3</sub>N, instead of Cs<sub>2</sub>CO<sub>3</sub> 15 13 DMF, instead of DMSO 72 14 15 CH<sub>3</sub>CN, instead of DMSO 50 16 Acetone, instead of DMSO 66 17 DCM, instead of DMSO 18

<sup>a</sup>Conditions: 1.0 equiv. 4'-bromoacetophenone 1, 2.0 equiv. methyl 4hydroxycinnamate 2, 3.0 equiv. base [0.10 M]; all solvents were rigorously degassed by freeze/pump/thaw. <sup>b</sup>Isolated yields by chromatography.

(entries 2 and 3). Irradiating with a 23 W compact fluorescent light (CFL) bulb or a 30 W white LED lamp resulted in a drop in yields (entries 4 and 5). The in situ formed phenolate anion of 2 was essential for this transformation because the reaction was completely inhibited without the base  $Cs_2CO_3$  (entry 6). Spectroscopic investigations confirmed that 2 was completely deprotonated by Cs<sub>2</sub>CO<sub>3</sub> (See supplementary information note 1<sup>+</sup>). Finally, a survey of bases including inorganic and organic bases (KHCO<sub>3</sub>, Na<sub>2</sub>CO<sub>3</sub>, K<sub>2</sub>CO<sub>3</sub>, K<sub>3</sub>PO<sub>4</sub>, DBU, TMG, and Et<sub>3</sub>N) and other solvents (DMF, acetone, CH<sub>3</sub>CN, and DCM) were not comparable to the combination of Cs<sub>2</sub>CO<sub>3</sub> and DMSO (entries 7-17).

### Substrate scope

We then evaluated the synthetic potential of this photochemical Heck-type arylation strategy. As detailed in Figure 1, various (hetero)aryl halides including iodides, bromides and chlorides were successfully coupled to 2. In general, aryl iodides displayed reactivity higher than that of aryl bromides and chlorides with shorter reaction time (3 - 8). It is noteworthy that the activation of aryl chlorides by transitionmetal complex is full of challenge and is normally conducted under high temperature due to the inertness of C – Cl bond.<sup>22</sup> We observed that the aryl chlorides also afforded the corresponding products in good yields under the mild photochemical Heck-type arylation conditions (3-8). Moreover, the site of the substitution on the aromatic ring had no detrimental effects on this photochemical transformation, and the o-, m- and p- substituted aryl halides were found be good substrates (6 - 8). For those electron-neutral and electron-rich aryl iodides, longer reaction times were needed and relatively lower yields were obtained that were attributed to the

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Figure 1. Substrate scope of (hetero)aryl halides. General conditions: (hetero)aryl halide (0.10 mmol), 2 (0.20 mmol), Cs<sub>2</sub>CO<sub>3</sub> (0.30 mmol), and DMSO (1.0 mL). Isolated yields were reported. *E/Z* ratio was measured by <sup>1</sup>H NMR.

associated slow electron transfer processes (9 - 16). However, their bromides or chlorides did not afford products under standard reaction conditions, which might due to their much lower reduction potentials.<sup>7d, 13, 23</sup> Overall, this photochemical Heck-type arylation method was compatible with aryl halides containing a wide range of functional groups, including -COCH<sub>3</sub> (3), -CHO (4), -CO<sub>2</sub>Me (5), -CN (6-8), -NHAc(12), -NH<sub>2</sub> (13), -OH (14 and 15), -COOH (16 and 17), and -NO<sub>2</sub> (18), providing a useful handle for subsequent functionalization and diversification of corresponding products. We next evaluated the activation of polycyclic aromatic hydrocarbon halides, and found that naphthalene (19 and 20), fluorene (21), anthracene (22), and phenanthrene (23) were efficient coupling partners. In addition, this newly developed system were also extended to various biologically important heterocyclic aryl halides, which are ubiquitous among pharmaceutical products. Heterocycles such as pyridine (24 and 25), isoquinoline (26 and 27), quinoline (28 and 29), pyrazine (30), thiophene (31) and carbazole (32) were readily used as radical precursors and provided the desired products with good yields.

Next, we extended the substrate scope to other vinylphenols (Figure 2). Under the standard conditions, vinylphenols with different electron-withdrawing substituents on the double bond, including thioester (33), amide (34), and ketone moieties (35 - 37), proceeded smoothly and gave the Heck-type arylation products in good to excellent yields. Notably, this transformation was not only limited to electron-withdrawing groups, the non- (38), alkyl- (39) and aryl- (40) substituted vinylphenols were also found to be compatible with this reaction system. This approach even enabled the regiospecific and stereoselective synthesis of the congested tetra-substituted olefin 41. In addition, a series of substituents on the aromatic ring were well tolerated (42 - 45), and this photo-induced process was also effective for substrates with the phenolic hydroxyl positioned meta (46) or ortho (47) to the double bond. In order to demonstrate the practicability of this transformation, we further evaluated the method for latestage functionalization applications of natural products. The

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Figure 2. Substrate scope of vinylphenol derivatives. General conditions: 1 (0.10 mmol), vinylphenol (0.20 mmol), Cs<sub>2</sub>CO<sub>3</sub> (0.30 mmol), and DMSO (1.0 mL). Isolated yields were reported. *E/Z* ratio was measured by <sup>1</sup>H NMR.

methods for arylation on the Cring of flavonoids are limited and multiple steps procedures were involved including the Pdcatalyzed Suzuki coupling with aromatic boronic acids<sup>24</sup> or the Pd- catalyzed Negishi coupling by a Lewis acid-triggered zincation.<sup>25</sup> We found that coumarin (48) and flavonoid (49 - 52) derivatives were easily arylated with the photochemical protocol in one step and the products were afforded with good yields. The natural products with additional carbohydrate appendixes, such as the pharmaceutical ingredients chlorogenic acid (53), esculin (54), and scutellarin (55), were also directly arylated under standard conditions without any protection procedures. The aryl chlorides were also tested as the aryl reagents, and the corresponding arylted products were obtained in moderate yields (48 - 53).

### Mechanistic investigation

Previously, we reported a visible light-induced  $\alpha$ -arylation of oxindole through the formation of electron-donor-acceptor (EDA) complex between oxindole enolate and (hetero)aryl halide.<sup>26</sup> The formation of EDA complex was unambiguously confirmed by a significant bathochromic shit in the UV-vis spectra when mixed the solution of oxindole enolate with (hetero)aryl halides. Therefore, we originally proposed that a similar photon-absorbing EDA complex between the phenolate anion of **2** and aryl halide **1** was formed to enable the arylation. However, we found that the colorless solution of vinylphenol 2(orange line in Figure 3a) was immediately turned to a bright yellow color upon addition of Cs<sub>2</sub>CO<sub>3</sub> in the absence of aryl halide 1 (blue line in Figure 3a). Moreover, we did not observe any color change after the aryl halide 1 was added to the solution of phenolate anion of 2 (red line in Figure 3a, perfectly overlapped with the absorption of the phenolate anion of 2). These results excluded the formation of a ground-state EDA complex association with the phenolate anion of 2 and aryl halide 1,<sup>18, 27</sup> but indicated that the photon-absorbing ability of the phenolate anion of 2 in the visible spectral region was responsible for triggering the aryl radical from its halide 1.

To better understand this process, we investigated the photo-physical behaviors of the phenolate anion of 2. The redox potential of the excited phenolate anion of 2 was estimated as -2.48 V vs. SCE on the basis of electrochemical and spectroscopic measurements (See supplementary information note 3<sup>+</sup>). Therefore, the reduction of 4'-bromoacetophenone 1 (-1.83 V vs. SCE in DMSO, see supplementary information Fig.  $7^{+}$ ) by the excited phenolate anion of **2** is thermodynamically feasible. Furthermore, a series of Stern-Volmer quenching studies revealed that the excited state of the phenolate anion of 2 was effectively quenched by the aryl halide1 (Figure 3b). The addition of radical inhibitor (2,2,6,6-Tetramethylpiperidin-

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Figure 3. a, UV/Vis absorption spectra of DMSO solutions (0.10 M) of 1, 2, mixture of 2 and  $Cs_2CO_3$ , and mixture of 1, 2 and  $Cs_2CO_3$ . b, Quenching of the phenolate of 2 emission (5 × 10<sup>-5</sup> M in DMSO) in the presence of increasing amounts of 1. c, Proposed mechanistic pathway.

1-yl)oxyl (TEMPO) or electron-transfer scavenger 1,4dinitrobenzene strongly inhibited the photochemical Heck-type arylation reaction, which indicated that a radical pathway proceeding through a single-electron transfer (SET) process was highly possible in this reaction.

On the basis of these observations, we proposed the possible mechanism as depicted in Figure 3c. The methyl 4hydroxycinnamate 2 was deprotonated by Cs<sub>2</sub>CO<sub>3</sub> to generate the colored phenolate anion A, which reached an electronically excited state (A\*) under the blue-light irradiation. Then a SET process from the excited phenolate anion A\* to 4'bromoacetophenone 1 occurred to produce a phenoxyl radical B and an aryl radical C. The latter was confirmed by the isolation of compound 56 during the TEMPO trapping experiments (See supplementary information note 5<sup>+</sup>). There were two possible pathways to generate the arylation product 3. The first one might be the direct coupling between the delocalized phenoxyl radical **B** and aryl radical **C**, while the second one would be the addition of radical C to another molecule of phenolate anion A to afford the radical anion intermediate D. In the TEMPO trapping experiments, we also isolated the compound 57, which was generated by trapping the intermediate **D** with TEMPO, and thus confirmed the second pathway (See supplementary information note 5<sup>+</sup>). The quantum yield for the model reaction was determined to be  $\Phi = 0.58$  (see supplementary information note 6<sup>+</sup>), indicating that the reported arylation reaction was a non-chain process<sup>28</sup> or an inefficient chain process.<sup>29</sup> Therefore, the subsequent pathways can be diverted into two types. In path a, the radical anion intermediate **D** might transfer a hydrogen to the radical **B** to afford the arylation product **3** and

recycle the methyl 4-hydroxycinnamate **2**. Path b includes a SET process between the radical anion intermediate **D** and 4'-bromoacetophenone **1** to give **3** and regenerate aryl radical **C** through a chain mechanism.

### Conclusions

In summary, this study established the ability of vinylphenolate anions to function as a strong reducing photoactivator to activate a broad range of aryl and heteroaryl halides, including iodides, bromides, and chlorides, when irradiated by visible light at room temperature. The resulting aryl radical engaged in a redox-neutral photochemical Heck-type arylation reaction that could not be realized by previous known visible light-induced photoredox processes. This method allows for the installation of aryl and heteroaryl units on vinylphenols with high regiospecificity and stereoselectivity and tolerates a wide range of functional groups. Furthermore, the potential utility of this transformation has been demonstrated by late-stage functionalization of complex natural products.

### Conflicts of interest

There are no conflicts to declare.

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