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Organophotoredox-Catalyzed Three-Component Coupling of Heteroatom Nucleophiles, Alkenes, and Aliphatic Redox Active Esters

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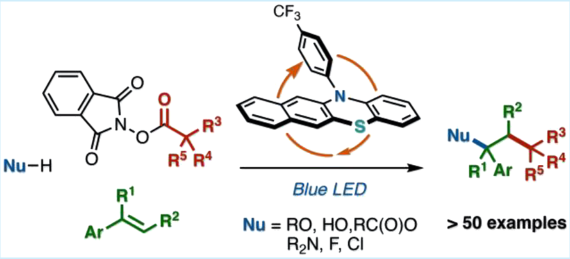
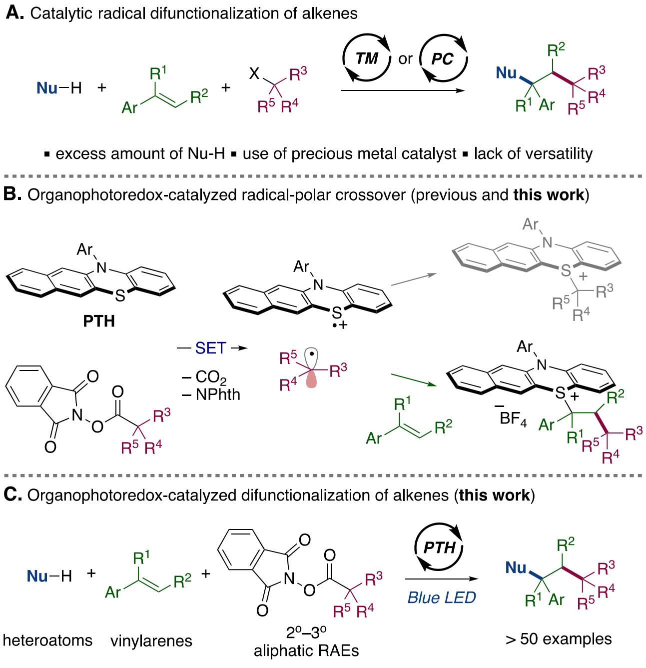
ABSTRACT: This manuscript describes a visible-light-mediated organophotoredox catalytic process for vicinal difunctionalization of alkenes using heteroatom nucleophiles and aliphatic redox active esters. A wide range of heteroatom nucleophiles including alcohols, water, carboxylic acids, amides, and halogens can be used for this reaction. This radical relay type reaction allows forging of $C(sp^3)-C(sp^3)$ with a carbon-centered radical and $C(sp^3)$−heteroatom bonds with a benzyl cation on the vinylarenes with complete regioselectivity in a single step.



Against a background of interest from the medical community and an increasing demand for bioactive natural products with $C(sp^3)$-rich frameworks, much attention has been given to the rapid and efficient construction of novel bioactive molecules.[1] Vicinal difunctionalization of alkenes has been identified as one of the preferred approaches for preparation of such molecules from readily available materials. Due to the ubiquity of heteroatom functional groups in drug molecules, vicinal difunctionalization of alkenes, which simultaneously incorporate a carbon group and a heteroatom group onto a carbon−carbon double bond, is highly desirable. In this context, a number of vicinal difunctionalizations of alkenes using transition-metal catalysts have been reported.[2] However, the reported protocols could not cover an alkyl group as a carbon source due to the instability of alkyl halides under highly basic reaction conditions[2b] and the lack of appropriate alkylating reagents.[2d]

As a complementary approach, radical relay-type alkylative difunctionalization of alkenes has been introduced (Scheme 1A).[3] Therein, a transition-metal catalyst facilitates the generation of a carbon radical via a single electron transfer (SET) to the radical precursor. The resultant alkyl radical undergoes an addition reaction across the alkene moiety to produce the relatively long-lived carbon radical, which is oxidized to the carbocation by the transition-metal catalyst which is then intercepted by heteroatom nucleophiles. However, suitable alkyl radical precursors have been limited to specific substrates possessing relatively low reduction potentials, such as alkyl diacyl peroxides,[4] α-halocarbonyls,[5] and hypervalent iodine reagents.[6] Recently, a visible-light photoredox catalyst enabled the radical relay difunctionalization of alkenes and dramatically expanded the scope of radical precursors.[7−9] Although significant progress has been made in this area,

Scheme 1. Radical Difunctionalization of Alkenes



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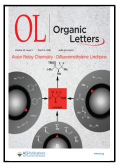


currently available methods still require the use of precious transition metals including Ru- or Ir-based photoredox catalysts. Additionally, one of the most serious problems is the lack of a general and powerful synthetic protocol that permits the use of a wide range of heteroatom nucleophiles.

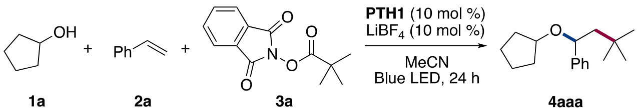
Previously, we reported the organophotoredox-catalyzed decarboxylative cross-coupling of aliphatic carboxylic acid derived redox active esters and aliphatic alcohols (Scheme 1B).[10,11] The reaction involves a SET from the excited state of the phenothiazine (PTH) catalyst to a redox active ester,[12] resulting in the formation of a PTH radical cation and an alkyl radical, which is liberated from the redox active ester. The resultant carbon centered-radical is oxidized by the PTH radical cation to the corresponding carbocation intermediate (Scheme 1B, top), which couples with various heteroatom nucleophiles. It was speculated whether the addition of the carbon-centered radical to an alkene could be performed before the oxidation process to accomplish three-component coupling (Scheme 1B, bottom).[13]

Herein, we report a visible-light-mediated organophotoredox catalysis process for vicinal difunctionalization of alkenes (Scheme 1C). This protocol facilitates assembly, in a single step, of aliphatic acid derived redox active esters, alkenes, and various heteroatom nucleophiles, such as alcohols, water, carboxylic acids, amides, and halogens, into densely functionalized hydrocarbons.

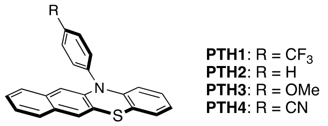
The alkyletherification of styrenes was commenced with aliphatic alcohols and aliphatic redox active esters. Previous methods for alkyletherification of alkenes require the use of excess amounts of alcohol nucleophiles (>5.0 equiv) and transition metal catalysts.[4f,5b,14] Additionally, the use of a tertiary alcohol as a nucleophile is not well developed.[5b,14a,b] To address these issues, the reaction conditions and scope of the substrates were carefully evaluated. Based on a previous report,[9] π-extended benzo[*b*]phenothiazine derivatives were used as an organophotoredox catalyst for this three-component coupling. After a quick screening, the combination of **PTH1**, featuring a benzo[*b*]phenothiazine core and a *p*-CF_3-phenyl substituent on the nitrogen, and $LiBF_4$ was found to be best for the reaction (Table 1, entry 1).[15] The effect of the *N*-substituent of the catalyst was next investigated. Use of H and OMe groups instead of a CF_3 group resulted in a slightly diminished product yield (entries 2 and 3). **PTH4** bearing a cyano group exhibited comparable reactivity (entry 4). The representative Ir- or Ru-based photoredox catalysts did not improve the product yield (entries 5−8). **PTH1** exhibited higher reactivity than **PTH4** when the reaction time was shortened to 12 h (entries 9 and 10). Finally, lowering the catalyst loading to 1 mol % and decreasing the reaction time to 2 h did not affect the product yield (entry 11).

Using the optimal reaction conditions, the scope of each ingredient was evaluated. First, the scope of the redox-active esters was explored (Scheme 2, top). Dimethyl-based tertiary redox-active esters having acetoxy and benzyloxy groups afforded the corresponding dialkyl ethers in moderate yields (**4aab** and **4aac**). Additionally, a tertiary alkyl group containing diethyl and cyano groups was introduced to the alkene (**4aad**). 1-Methylcyclopentyl and 1-methylcyclohexyl substituents were efficiently incorporated (**4aae** and **4aaf**). A heteroatom-fused aliphatic ring system was amenable to this three-component coupling (**4aag** and **4aah**). A sterically hindered adamantyl redox active ester could participate in this reaction (**4aai**). Secondary carboxylic acids were also found to be suitable alkyl sources (**4aaj**−**4aal**). Unfortunately, the reactions with primary aliphatic redox-active esters did not afford any product (data not shown). This might be due to inefficient formation of the alkyl radical and slow radical addition to the alkenes.

Table 1. Screening of Reaction Conditions[a]



Entry	Change from standard conditions	Yield of **4aaa** (%)[b]
1	none	62
2	**PTH2** instead of **PTH1**	41
3	**PTH3** instead of **PTH1**	50
4	**PTH4** instead of **PTH1**	65
5	$Ir(ppy)_3$ (1 mol %) instead of **PTH1**	33
6	$Ru(bpy)_3(PF_6)_2$ (1 mol %) instead of **PTH1** and $LiBF_4$	13
7	$Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (1 mol %) instead of **PTH1** and $LiBF_4$	14
8	$Ir(ppy)_2(dtbbpy)PF_6$ (1 mol %) instead of **PTH1** and $LiBF_4$	23
9	**PTH4** instead of **PTH1**, 12 h	35
10	**PTH1**, 12 h	64
11[c]	**PTH1** (1 mol %), $LiBF_4$ (1 mol %), and 2 h	73 (60)

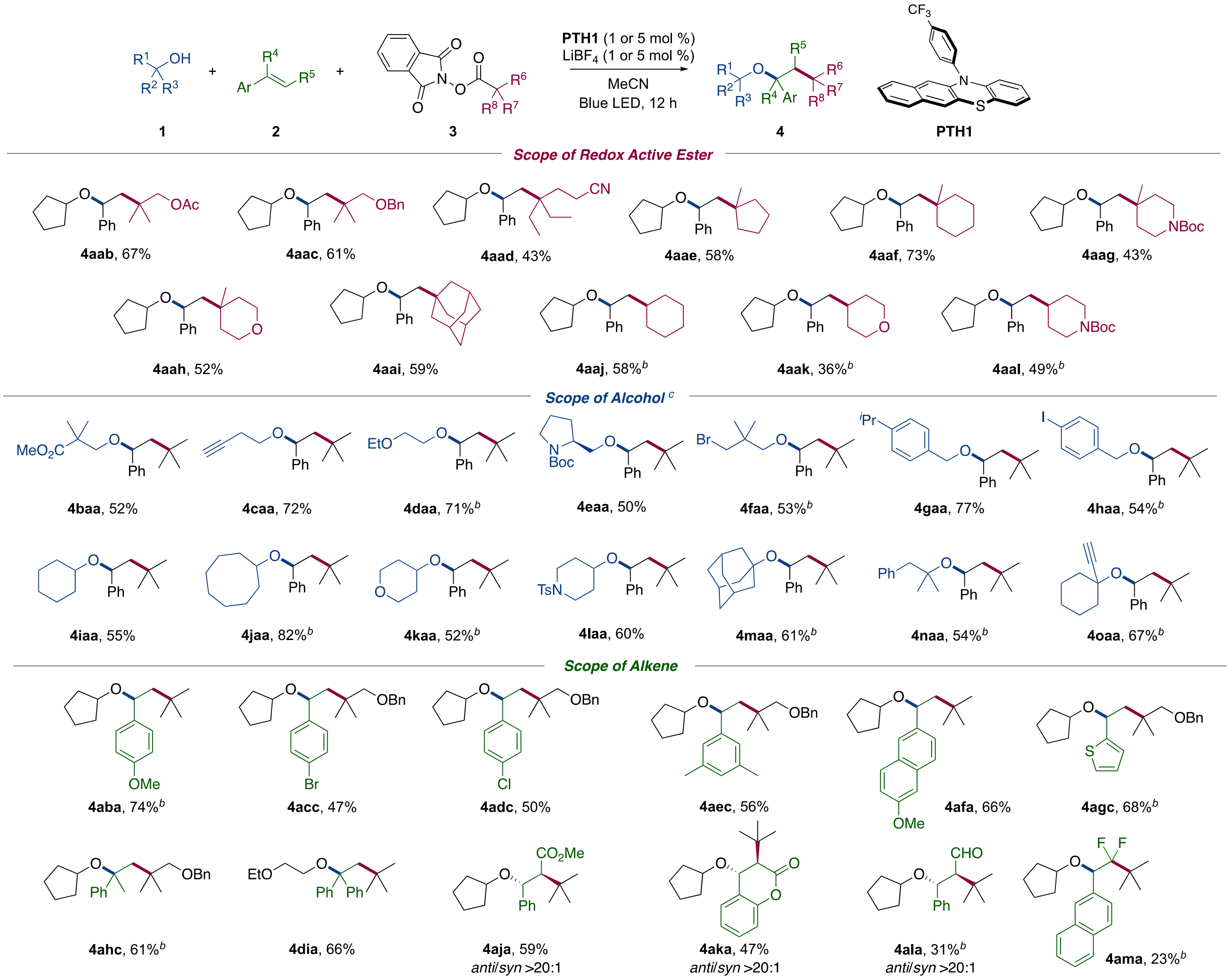


[a] The reaction was carried out with **1a** (0.6 mmol), **2a** (0.4 mmol), **3a** (0.2 mmol), **PTH** (0.02 mmol), and $LiBF_4$ (0.02 mmol) in MeCN (0.6 mL) under blue LED irradiation for 24 h. [b] ^1H NMR yield based on **3a**. Yield of the isolated product is in parentheses. [c] Reaction was carried out with **1a** (0.6 mmol), **2a** (0.2 mmol), **3a** (0.2 mmol), **PTH1** (0.002 mmol), and $LiBF_4$ (0.002 mmol) in MeCN (0.6 mL) under blue LED irradiation for 2 h.

The effect of various alcohol nucleophiles was examined (Scheme 2, middle). A broad range of functional group compatibility was observed with primary aliphatic alcohols. Ester, alkyne, ether, amide, and alkyl bromide groups did not inhibit the reaction (**4baa**−**4faa**). Benzyl ethers were obtained in good yields (**4gaa** and **4haa**). Although iodoarene is known to be reduced by the PTH catalyst, the compound survived in this system. Secondary aliphatic alcohols could also participate in this reaction (**4iaa**−**4laa**). It is noteworthy that the reaction with sterically hindered tertiary alcohols gave the desired dialkyl ether in high yield (**4maa**−**4oaa**).

Next, functionalized vinyl arenes were investigated (Scheme 2, bottom). A *p*-methoxy substituent on the aromatic ring was found to be compatible (**4aba**). Halogen substituents survived under reaction conditions without reduction (**4acc** and **4adc**). *m*-Substituents did not inhibit the reaction (**4aec**). Dialkyl ethers containing naphthalene and thiophene were obtained in moderate yields (**4afa** and **4agc**). When *α*-methyl or phenyl styrenes were subjected to the optimal reaction conditions, the corresponding tertiary benzylic dialkyl ethers were obtained (**4ahc** and **4dia**). When cinnamyl ester was used, regio- and diastereoselective $C(sp^3)-C(sp^3)$ and $C(sp^3)-O$ bond formation occurred to provide the synthetically valuable *β*-

Scheme 2. Substrate Scope[a]



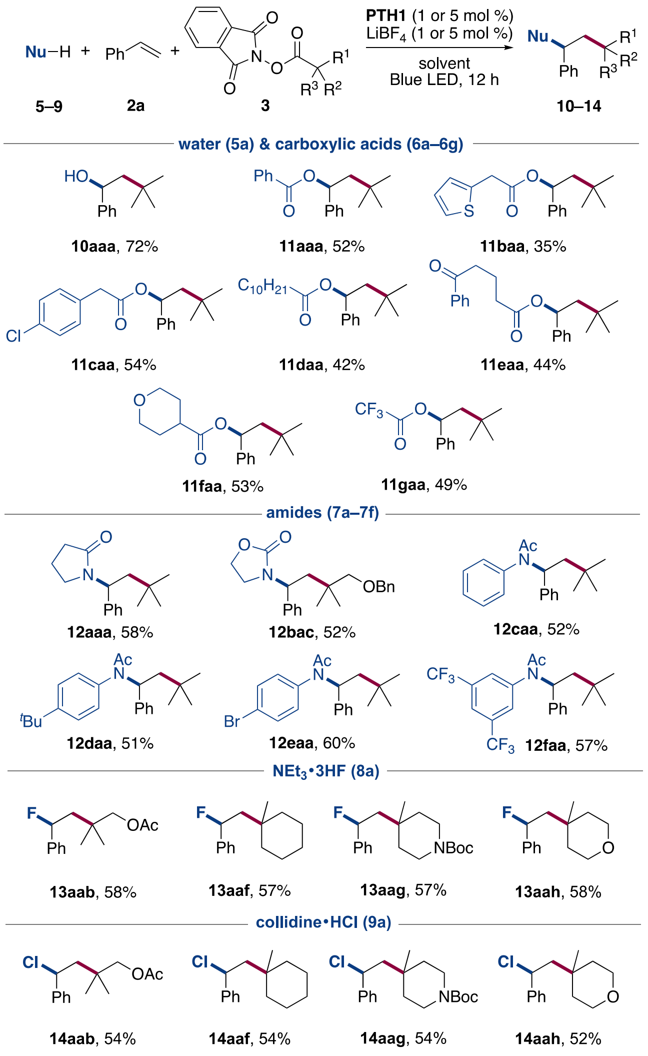
[a] The reaction was carried out with **1** (0.6 mmol), **2** (0.2 mmol), **3** (0.2 mmol), **PTH1** (0.002 mmol), and $LiBF_4$ (0.002 mmol) in MeCN (0.6 mL) under blue LED irradiation for 2 h. [b] The reaction conditions were modified. (see Supporting Information) [c] The reaction was carried out with **1** (0.6 mmol), **2** (0.4 mmol), **3** (0.2 mmol), **PTH1** (0.01 mmol), and $LiBF_4$ (0.01 mmol) in MeCN (0.6 mL) under blue LED irradiation for 6 h.

alkoxylcarbonyl compound (**4aja**). Coumarin also exhibited high regio- and stereoselectivity (**4aka**). Both cinnamaldehyde and *β*,*β*-difluoroalkene were employed to provide the corresponding functionalized molecules, respectively (**4ala** and **4ama**).

To demonstrate the versatility of this oraganophotoredox catalysis, reactions with other heteroatom nucleophiles were examined (Scheme 3). After a quick screening, it was found that various heteroatom nucleophiles were applicable. A water participated in the reaction to afford the alkylhydroxylation product (**10aaa**). Carboxylic acids were also applicable as oxygen nucleophiles to provide benzyl ester derivatives.[16] Aromatic, benzylic, primary, and secondary alkyl carboxylic acids were successfully introduced (**11aaa**−**11faa**). The trifluoroacetoxylated product was also obtained (**11gaa**). Next, nitrogen nucleophiles were investigated. Both cyclic amide and carbamate acted as good nucleophiles (**12aaa** and **12bac**). Acetyl-protected anilines were also found to be suitable substrates (**12caa**−**12faa**).

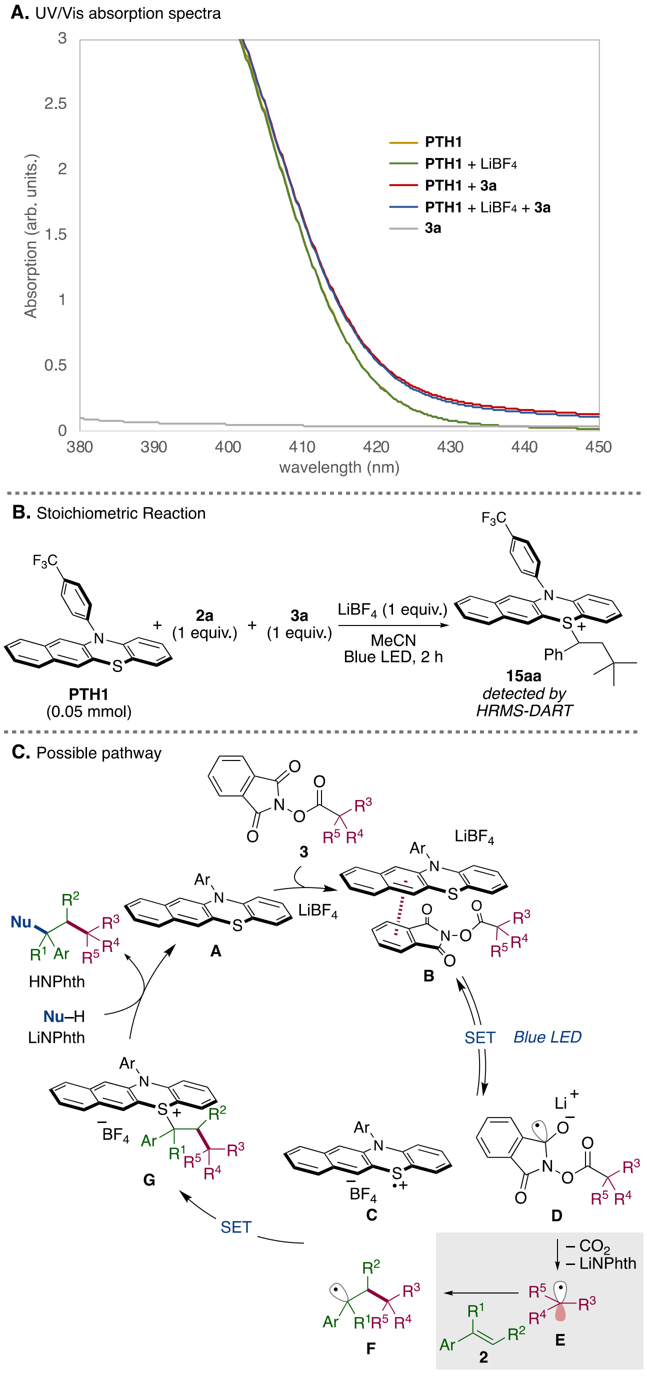
The scope of the nucleophiles could be expanded to include fluoride and chloride anions (Scheme 3). Although catalytic alkylfluorination of alkenes using the fluoride anion has been reported,[4d17] the incorporation of a tertiary alkyl group without using transition metals is a noteworthy feature of the present protocol. Screening of the fluoride anion revealed that triethylamine trihydrofluoride ($NEt_3{\cdot}3HF$) was identified to be the best source. An acyclic or cyclic tertiary alkyl group and a fluorine atom were efficiently introduced to an alkene with complete regioselectivity (**13aab**−**13aah**). In contrast to the alkylfluorination, alkylchlorination with a chloride anion has received less attention.[18] Following the alkylfluorination, triethylamine hydrochloride was used as a chloride anion source, but the desired product was obtained in 8% yield with formation of the E2/E1 product. To avoid the elimination reaction induced by a conjugate base, a bulky collidine hydrochloride salt was selected. This approach resulted in a dramatic improvement in the product yield, providing a series of benzyl chlorides in high yield (**14aab**−**14aah**).

Scheme 3. Scope of Other Heteroatom Nucleophiles[a]



[a]The reaction was carried out with **5–9** (0.6 mmol), **2a** (0.2 mmol), **3a** (0.2 mmol), **PTH1** (0.002 or 0.01 mmol), and $LiBF_4$ (0.002 or 0.01 mmol) in solvent (see Supporting Information) under blue LED irradiation for 12–24 h.

Scheme 4. Mechanistic Studies



In an attempt to clarify the reaction mechanism, the following experiments were conducted. First, the SET from the **PTH1** catalyst to a redox active ester was investigated. It is well-known that redox active esters tend to form electron-donor–acceptor (EDA) complexes with electron-rich organic molecules, hence facilitating SET.[19] To confirm the intermediacy of the EDA complex, the UV/vis absorption spectra for various combinations of reaction components were measured under identical concentrations to that for the optimal reaction conditions (Scheme 4A). As a result, a significant red shift of the absorption band was observed when **PTH1** and the redox active ester **3a** coexisted. This finding indicated the involvement of an EDA complex in the initial photoactivation step.[20]

Next, possible mechanisms for the nucleophile substitution step were considered. There are two plausible reaction pathways, an S_N2 type reaction with a benzylsulfonium intermediate or an S_N1 type reaction with a benzyl cation.[20] In an attempt to monitor the benzylsulfonium intermediate, the reaction was carried out under stoichiometric conditions without a heteroatom nucleophile. Then, the corresponding benzylsulfonium (**15aa**) was detected by direct analysis using real time-high resolution mass spectrometry (HRMS-DART). Density-functional theory (DFT) calculations indicated that the Gibbs free energy of the benzylsulfonium intermediate was lower than that of the benzyl cation (see Supporting Information). These results suggested that the benzylsulfonium was the dominant species in the nucleophilic substitution step.

Based on the mechanistic studies depicted above, the proposed mechanism for the organophotoredox-catalyzed difunctionalization of alkenes is outlined in Scheme 4C. The catalytic cycle begins with a photoinduced SET within the EDA complex (**B**) composed of the PTH catalyst (**A**) and redox active ester **3** which results in the production of the PTH radical cation (**C**) and the radical anion form (**D**) of the redox active ester. The radical anion **D** then collapses to afford the corresponding alkyl radical (**E**) and the phthalimide anion with release of CO_2. The addition of the alkyl radical **E** to vinylarene **2** produces the relatively long-lived benzyl radical (**F**) ($E_{1/2}$ = 0.23 V vs SCE),[21] which couples with the PTH radical cation **C** ($E_{1/2}$ = 0.87 V vs SCE)[9] through single-electron oxidation followed by complexation to produce the benzylsulfonium intermediate (**G**). Finally, **G** is intercepted by a heteroatom nucleophile to give the dialkyl ether and regenerate **A**. The role of $LiBF_4$ as an additive would be to facilitate acceleration of the SET from PTH to the redox active esters.

In summary, visible-light-mediated organophotoredox catalysis afforded a versatile protocol for vicinal difunctionalization of alkenes. This protocol permitted the assembly of readily available, various heteroatom nucleophiles, vinylarenes, and aliphatic acid derived redox active esters into highly functionalized $C(sp^3)$-rich motifs. Nitrogen, oxygen, and halogen nucleophiles functioned as nucleophiles without the requirement to be in excess. Transition-metal-free and mild reaction conditions are attractive features of this protocol. Extending this approach to other multicomponent couplings is ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00211.

Experimental details and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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