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Visible-Light Photoredox-Catalyzed Hydroalkoxymethylation of Activated Alkenes Using α-Silyl Ethers as Alkoxymethyl Radical Equivalents

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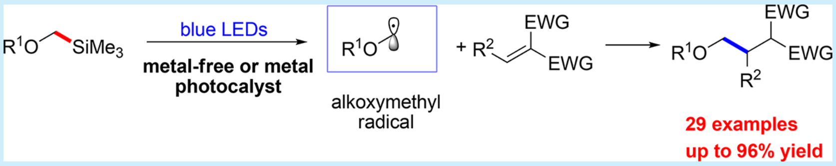
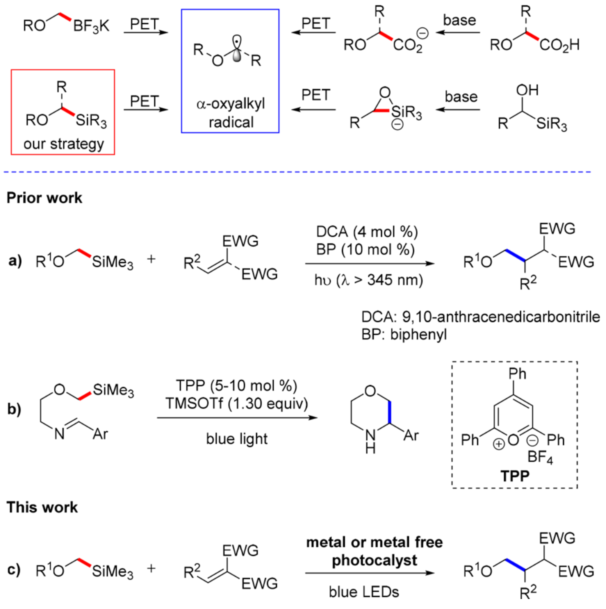
Supporting Information



ABSTRACT: A new neutral silicon-based traceless activation group (TAG) for visible-light photoredox-catalyzed hydroalkoxymethylation of alkenes is presented. This reaction involves in-situ-generated alkoxymethyl radical via single electron oxidation (SET) of α-TMS-substituted ethers, followed by subsequent conjugate addition to activated alkenes. Various functional groups were tolerated both under mild metal and metal-free conditions to provide good to excellent yields. Furthermore, the addition products were transformed to valuable synthetic building blocks, such as carboxylic acids, γ-butyrolactones, and complex aryl alkyl ethers.

α-Alkoxyalkyl radicals are useful reaction intermediates in C−C bond forming reactions for functionalization of ethers,[1] which represent an important structural motif in many solvents, natural products, and pharmaceuticals. Since α-oxyalkyl radicals act as nucleophiles[2] with electrophiles such as alkenes, alkynes, imines, and aldehydes, many methods utilizing such species have been developed, because of their significant importance. An efficient strategy for the generation of α-alkoxyalkyl radicals is direct C−H activation of the α-hydrogen in ethers. Conventional research has focused on the generation of α-alkoxyalkyl radicals by radical initiators, oxidants, γ-ray irradiation, or electrochemical promotion;[3] however, these methods use stoichiometric oxidants and high-energy light sources. To overcome these problems, suitable alternative protocols are in high demand and are desirable for synthetic organic chemists. Recently, visible-light photoredox catalysis has been a useful tool for many organic transformations,[4] in particular in the field of single-electron redox chemistry. However, the direct single electron oxidation of ethers by visible-light photoredox catalysis remains difficult, because of the higher oxidation potential of the corresponding ethers (e.g., $E^{\mathrm{ox}}_{1/2} > +2.4$ V vs SCE for THF, THP, and Et$_2$O).[5] Recently, this problem was solved by merging photoredox catalysts with hydrogen atom transfer (HAT) reagents such as thiols and persulfate.[5c,6] Although these methods can directly generate α-alkoxyalkyl radicals, they are limited by the need of an excess of ether. Alternatively, the introduction of a traceless activation group (TAG) at the α-carbon of an ether can significantly decrease the oxidation potential necessary to achieve direct and selective oxidation of ethers by photoredox catalysis without any co-catalyst. Recently, potassium trifluoroborates,[7] in-situ-generated carboxylates,[8] and hypervalent silicon anions[9] have been developed as traceless activation groups of ethers for oxidative generation of α-oxyalkyl radicals via photoinduced electron transfer (PET), as shown in Scheme 1. Although these TAGs for ethers assist in the generation of α-

Scheme 1. Oxidative Generation of α-Oxyalkyl Radical via PET



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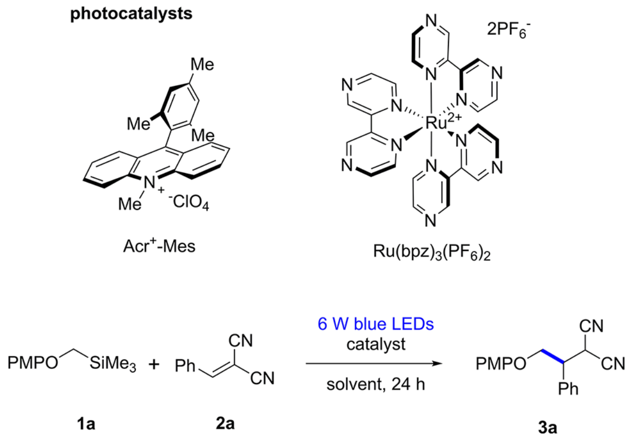
oxyalkyl radicals and then react with electrophiles to form new C−C bonds, they are in salt form or in-situ-generated by stoichiometric base additives.

Therefore, the development of neutral TAGs is still needed. Neutral alkylsilane[10] at the α-carbon of ethers also decreases the oxidation potential by stabilization of the cation radical intermediate by overlap of the filled C−Si bond with the half-vacant 2p orbital of the oxygen (β-silicon effect).[5a] In addition, α-silyl-substituted ethers are easily synthesizable, inexpensive, and easy to handle. Indeed, we became interested in utilizing alkylsilane as a neutral TAG for ether functionalization. In 1998, the Steckhan group first reported an ultraviolet (UV)-light-mediated generation of α-alkoxymethyl radical from α-silyl ethers using 9,10-anthracenedicarbonitrile and biphenyl as photoredox catalysts and its coupling with electron-deficient alkenes (see Scheme 1a).[11] Although this result provided a new concept for neutral silane TAGs, the reaction suffered from poor yields, limited substrate scope, and the requirement of a high-energy source (UV range). More recently, Bode and co-workers developed a new synthetic method for producing *N*-heterocycles by in situ generation of α-alkoxymethyl radicals via oxidative single-electron oxidation, followed by rapid desilylation and subsequent intramolecular cyclization using 2,4,6-triphenylpyrylium tetrafluoroborate (TPP) as a photoredox catalyst (Scheme 1b).[12] To the best of our knowledge, the formation of α-alkoxymethyl radicals from TMS-modified ethers by visible-light-mediated photoredox catalysis and its subsequent intermolecular coupling with activated alkenes has not been described. Herein, we report the visible-light photoredox-catalyzed hydroalkoxymethylation of activated alkenes using α-TMS-substituted ethers as α-alkoxymethyl radical equivalents (see Scheme 1c).

In our initial study, PMPOCH$_2$TMS **1a** was chosen as an α-alkoxymethyl radical surrogate. By the above-mentioned β-silicon effect, the oxidation potential of PMPOCH$_2$TMS **1a** was measured as +1.1 V vs SCE in MeCN, which is lower than the corresponding alkyl ether. We expected the high oxidation ability of photoredox catalyst ($E_{1/2}^{red}$ (PC*/PC$^{\bullet -}$) > +1.1 V vs SCE) would be necessary to oxidize PMPOCH$_2$TMS **1a**.[13] First, we focused on metal-free conditions, because they have advantages over transition-metal conditions (e.g., residual metal problems, price, etc.).[4e,f] The reaction of PMPOCH$_2$TMS **1a** with benzalmalononitrile **2a** was first performed in MeCN using 1 mol % organic photoredox catalyst under irradiation with 6 W blue LEDs. As expected, the desired hydroalkoxymethylation product **3a** was obtained in 9% yield, using Fukuzumi acridinium salt (Acr$^+$-Mes)[14] with strong oxidizing power (Table 1, entry 1), while other organic photocatalysts with weaker oxidizing power did not react (see details in the Supporting Information). We investigated further to optimize the reaction conditions, keeping other parameters unchanged. The influence of solvent on the reaction efficiency was significant. Especially, a MeOH/CH$_3$CN co-solvent provided an excellent yield of **3a** in 82% yield (Table 1, entry 9). In addition, when the amount of benzalmalononitrile **2a** and the catalyst loading were reduced, the yields were unfortunately reduced (Table 1, entries 10−12). After a thorough screening of the reaction conditions, the best result was achieved by reaction of PMPOCH$_2$TMS **1a** and 2.0 equivalents of benzalmalononitrile **2a** in the presence of 1.0 mol % of Acr$^+$-Mes in CH$_3$CN/MeOH at room temperature, being irradiated with 6 W blue LEDs under an argon atmosphere to furnish the desired product **3a** in 82% yield (Table 1, entry 9). Next, we expanded our research to find transition-metal-based photocatalysts to perform the same transformation. Transition-metal-based catalysts such as *fac*-Ir(ppy)$_3$, Ir(ppy)$_2$(dtb-bpy)PF$_6$, Ir(dF-CF$_3$ppy)$_2$(dtb-bpy)PF$_6$, Ru(bpy)$_3$Cl$_2$, and Ru(bpz)$_3$(PF$_6$)$_2$ were tested to perform the hydroalkoxymethylation.

Table 1. Optimization of the Reaction Conditions[a]



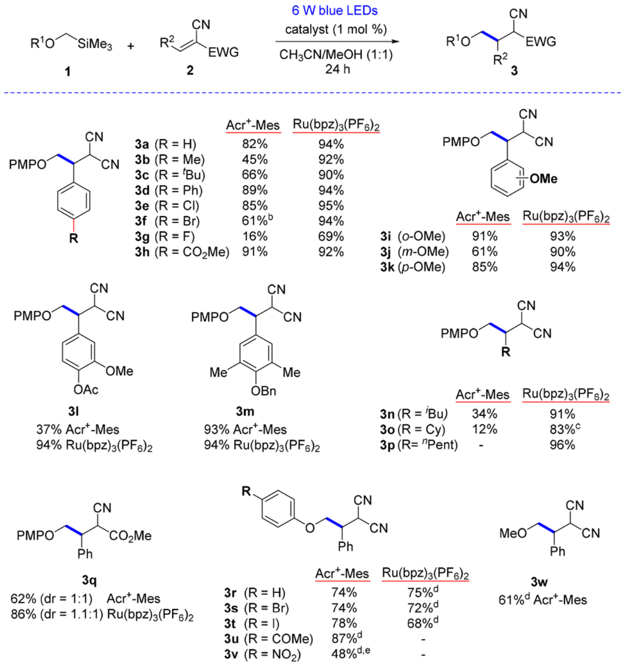
entry	catalyst (mol %)	2a (equiv)	solvent (0.1 M)	yield[b] (%)
1	Acr$^+$-Mes (1.0)	2.0	MeCN	9
2	Acr$^+$-Mes (1.0)	2.0	EtOAc	41
3	Acr$^+$-Mes (1.0)	2.0	DMF	29
4	Acr$^+$-Mes (1.0)	2.0	EtOH	53
5	Acr$^+$-Mes (1.0)	2.0	MeOH	64
6	Acr$^+$-Mes (2.0)	2.0	MeOH	66
7	Acr$^+$-Mes (1.0)	2.0	MeOH/Acetone (1:1)	65
8	Acr$^+$-Mes (1.0)	2.0	MeOH/EtOAc (1:1)	76
9	**Acr$^+$-Mes (1.0)**	**2.0**	**MeOH/MeCN (1:1)**	**82** (n.r.)[c]
10	Acr$^+$-Mes (0.5)	2.0	MeOH/MeCN (1:1)	58
11	Acr$^+$-Mes (1.0)	1.5	MeOH/MeCN (1:1)	68
12	Acr$^+$-Mes (1.0)	1.2	MeOH/MeCN (1:1)	50
13	Ru(bpz)$_3$(PF$_6$)$_2$ (1.0)	2.0	MeOH/MeCN (1:1)	96
14	Ru(bpz)$_3$(PF$_6$)$_2$ (1.0)	1.5	MeOH/MeCN (1:1)	93
15	**Ru(bpz)$_3$(PF$_6$)$_2$ (1.0)**	**1.2**	**MeOH/MeCN (1:1)**	**94** (n.r.)[c]
16	Ru(bpz)$_3$(PF$_6$)$_2$ (0.5)	1.2	MeOH/MeCN (1:1)	88

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (quantity noted), catalyst (quantity noted), solvent (0.1 M) with 6 W blue LEDs irradiation at room temperature for 24 h under argon in pressure tubes. [b]Isolated yield by flash column chromatography. [c]In the absence of light source or photocatalyst. n.r. = no reaction.

Surprisingly, coupling product **3a** was obtained in quantitative yield in the presence of Ru(bpz)$_3$(PF$_6$)$_2$, while other metal-based photocatalysts did not facilitate the reaction (Table 1, entry 13; see the Supporting Information). The amount of alkene **2a** was decreased, resulting in a slight decrease in yield to 94%, still an excellent result (Table 1, entries 14 and 15). Ultimately, reaction of PMPOCH$_2$TMS **1a** with 1.2 equivalents of benzalmalononitrile **2a** utilizing 1.0 mol % Ru(bpz)$_3$(PF$_6$)$_2$ was chosen as the transition-metal-based optimized conditions (Table 1, entry 15). It is notable that either in the absence of light or the photocatalyst under both catalytic conditions, the formation of product **3a** was not observed, which strongly supports the role of visible light in this reaction (Table 1, entries 9 and 15). We developed organic and metal-based photoredox catalyst systems for the hydroalkoxymethylation of alkene. Therefore, we explored various substrates using both catalysts for hydroalkoxymethylations.

Next, we explored the substrate scope of various primary α-silyl ethers with activated alkenes (see Scheme 2). Under both optimized conditions, PMPOCH$_2$TMS **1a** was added to a diverse range of benzalmalononitrile derivatives (**2a**–**2m**) to form aryl alkyl ethers (**3a**–**3m**) in good to excellent yields. In particular, bulky *tert*-butyl, phenyl-substituted (**2c**, **2d**), *o*-, *m*-, and *p*-MeO substituted- (**2i**–**2k**), and 3,4-disubstituted- and 3,4,5-trisubstituted (**2l**, **2m**) benzylidenemalononitriles were not influenced by steric hindrance in the addition reaction.

Scheme 2. Substrate Scope of Various Primary α-Silyl Ethers with Activated Alkenes[a]

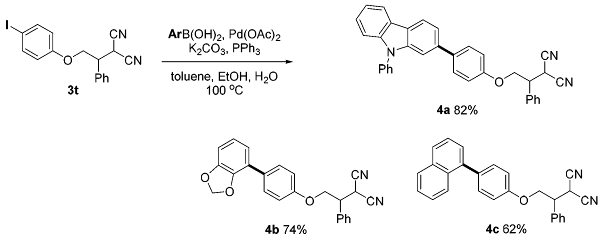


[a] Reaction conditions as given in Table 1, entries 9 and 15; reported yields are given for isolated material. [b] Catalyst (2 mol %). [c] Alkene **2o** (2.0 equiv). [d] Catalyst (5 mol %). [e] After 48 h. See the Supporting Information for details.

Halogen-containing benzalmalononitrile derivatives (**2e**–**2g**) gave slightly low yields with the exception of 4-chlorobenzalmalononitrile **2e** under metal-free conditions. However, the corresponding products of these lower-yielding reactions could be enhanced using $\mathrm{Ru(bpz)_3(PF_6)_2}$ as the photoredox catalyst. We extended the substrate scope to alkylidene malononitriles (**2n**–**2p**). Under metal-free conditions, the alkylidene malononitriles were less efficient than benzalmalononitrile derivatives for the photocatalyzed hydroalkoxymethylation reaction. As an alternative, $\mathrm{Ru(bpz)_3(PF_6)_2}$ was used as the photoredox catalyst, and the desired corresponding products (**3n**–**3p**) were obtained in excellent yields of 83%–96%. Instead of benzalmalononitrile derivatives, other alkene types, such as methyl (*E*)-2-cyano-3-phenyl acrylate **2q**, smoothly coupled with PMPOCH$_2$TMS **1a** to give the corresponding product **3q** in 62% yield and ~1:1 diastereomeric ratio (dr). Next, we expanded the substrate with various aryloxymethylsilanes **1** that have substituted H, Br, I, COMe, NO$_2$ in the aryl group, instead of a methoxy group to examine the electronic effect for desilylative coupling. Under the metal-free conditions, similar and less-efficient results were obtained. However, reactivity under the metal-catalyzed conditions was reduced, because $\mathrm{Ru(bpz)_3(PF_6)_2}$ is a weaker oxidant than Acr$^+$-Mes in the excited state from visible-light irradiation. Therefore, metal-based catalyst systems were less efficient at oxidizing the electron-neutral and electron-poor aryloxymethylsilanes (**1b**–**1f**). When the $\mathrm{Ru(bpz)_3(PF_6)_2}$ loading was increased, hydroalkoxymethylation of H and halogen-substituted aryloxymethylsilanes (**1b**–**1d**) proceeded smoothly, and the corresponding coupled product (**3r**–**3t**) was obtained in good yield. However, strong electron-withdrawing-group-substituted aryloxymethylsilanes (**1f**, **1e**) cannot oxidize via $\mathrm{Ru(bpz)_3(PF_6)_2}$. Hydroalkoxymethylation of (methoxymethyl)trimethylsilane also proceeded under metal-free conditions. This result shows that the develped method proceeds in both aryl ether and alkyl ether.

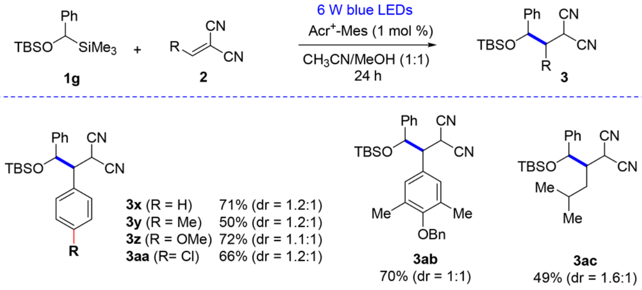
In addition, we conducted further functionalization of **3t** and gram-scale synthesis of **3a**. The **3t** smoothly underwent Suzuki coupling with arylboronic acids to provide moderate to good yields of the corresponding products (**4a**–**4c**) (see Scheme 3).[15] The **3a** was obtained in 1.22 g, 83% (Acr$^+$-Mes) and 1.42 g, 97% ($\mathrm{Ru(bpz)_3(PF_6)_2}$) yield (see details in the Supporting Information). Unfortunately, we have not been able to expand on hydroalkoxylmethylation with less-activated alkenes, such as acrylonitrile, methyl acrylate, α,β-unsaturated ketone and lactone, etc. under the optimized conditions.

Scheme 3. Further Functionalization of 3t



Next, we examined secondary α-silyl ethers in this reaction. TBS-protected secondary α-silyl ether **1e** was treated with various alkenes containing both electron-neutral, electron-donating, and halogen substituents. As illustrated in Scheme 4, all of the reactions provided moderate to good yields and ~1:1

Scheme 4. Substrate Scope of Secondary α-Silyl Ethers with Various Activated Alkenes[a]

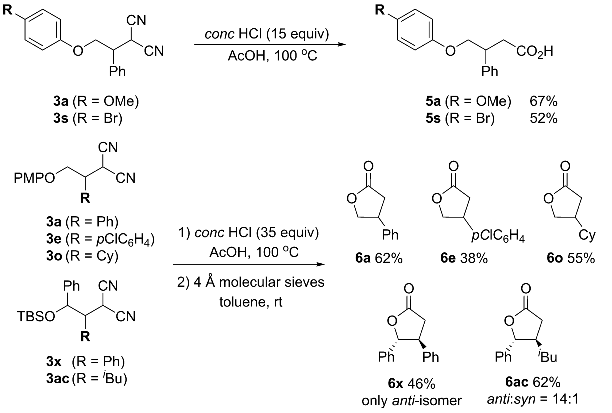


[a] Reaction conditions as given in Table 1, entry 9. See the Supporting Information for details.

dr under the optimized conditions. Unfortunately, the hydroalkoxylation of secondary α-silyl ethers with alkenes was not efficient under metal-catalyzed conditions, presumably because the TBS-protected α-silyl ether **1e** has a higher oxidation potential than PMPOCH$_2$TMS **1a**.

To demonstrate the efficacy of this protocol, the coupled products **3** were converted to useful synthetic building blocks (see Scheme 5). Carboxylic acid-containing aryl alkyl ethers (**4a**, **4s**) were obtained after acidic hydrolysis and decarboxylation in good yields. Notably, γ-butyrolactones,[16] which are very important synthetic core structures found in natural products and pharmaceuticals, were prepared from ethers **3** by acidic hydrolysis, decarboxylation, deprotection, and cyclization in good yields. The diastereomeric mixtures of ethers (**3x**, **3ac**) were converted to predominantly anti γ-butyrolactones (**6x**, **6ac**) by kinetic resolution in the lactonization.

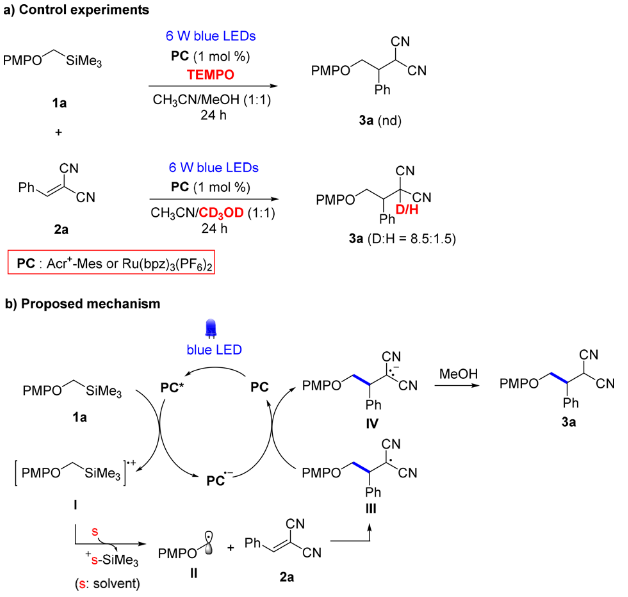
Scheme 5. Conversion of Ethers 3 to Useful Synthetic Building Blocks



To gain insight into the reaction mechanism, control reactions were performed under both catalyst conditions. In the Stern–Volmer luminescence quenching experiment, the excited state of the photoredox catalyst was quenched by PMPOCH$_2$TMS **1a** but was not quenched by benzalmalononitrile **2a**.

This result indicates that the SET mechanism between PMPOCH$_2$TMS **1a** and the excited photoredox catalyst occurs in the initial stage (as detailed in the Supporting Information). Next, radical trapping experiments were undertaken. The addition of TEMPO or γ-terpinene to the hydroalkoxymethylation completely suppressed the reaction, indicating that the reaction involves a radical process (Scheme 6a). Based on our control experiments and the literature,[5a,11,12] a plausible mechanism has been postulated in Scheme 6b. Single-electron oxidation of PMPOCH$_2$TMS **1a** by the excited photoredox catalyst (**PC***) produces cation radical species **I**, which rapidly converts to α-alkoxymethyl radical **II** in a desilylation process via solvent. This in-situ-generated α-alkoxymethyl radical **II** couples with benzalmalonitrile **2a** to generate stable α-cyano radical **III**. Further single-electron transfer from the reduced photoredox catalyst (**PC**$^{\bullet-}$) to its original state leads to the formation of α-cyano anion **IV**. Subsequent protonation of α-cyano anion **IV** with methanol provides the desired product **3a**. Control experiments using CH$_3$CN/CD$_3$OD instead of CH$_3$CN/CH$_3$OH as solvent were performed to confirm the proposed mechanism. As a result of the experiment, replacement of the hydrogen of product **3a** with deuterium was confirmed by ^{1}H NMR (Scheme 6a). In addition, we also performed on–off experiments to verify the proposed SET mechanism.

Scheme 6. Control Experiments and Proposed Reaction Mechanism



These results showed that sustained irradiation with visible light is essential for hydroalkoxymethylation to occur (see details in the Supporting Information).

In conclusion, we have developed a neutral silicon-based TAG for visible-photoredox-catalyzed hydroalkoxymethylation of alkenes. The addition reaction tolerates various functional groups and provides good to excellent yields under both metal and metal-free conditions. We proposed a reaction mechanism that involves in-situ-generated alkoxymethyl radical via single electron oxidation of α-TMS substituted ethers. Mechanistic studies support a radical pathway for a plausible reaction mechanism. Furthermore, the synthesized ether compounds were further transformed to valuable synthetic building blocks such as carboxylic acids, γ-butyrolactones, and complex aryl alkyl ethers.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02721.

> Electrochemical and photophysical measurements and mechanism studies; experimental procedures; spectroscopic data for all new compounds (^{1}H NMR, ^{13}C NMR, ^{19}F NMR, IR, HRMS), including images of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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