

A Triple Photoredox/Cobalt/Brønsted Acid Catalysis Enabling Markovnikov Hydroalkoxylation of Unactivated Alkenes

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Supporting Information Placeholder

ABSTRACT: We demonstrate Markovnikov hydroalkoxylation of unactivated alkenes using alcohols through a triple catalysis consisting of photoredox, cobalt and Brønsted acid catalysts under visible light irradiation. The triple catalysis realizes three key elementary steps in a single catalytic cycle: 1) Co(III) hydride generation by photochemical reduction of Co(II) followed by protonation, 2) metal hydride hydrogen atom transfer (MHAT) of alkenes by Co(III) hydride and 3) oxidation of the alkyl Co(III) complex to alkyl Co(IV). The precise control of protons and electrons by the three catalysts allows the elimination of strong acids and external reductants/oxidants that are required in the conventional methods.

Markovnikov hydroalkoxylation of alkenes with alcohols is a fundamental and atom-economical approach for the construction of synthetically valuable ethers from abundant and inexpensive materials. As described in every textbook on organic chemistry, an acid protonates the alkene to form the carbocation, which is then captured by an alcohol nucleophile (Scheme 1A, left).¹ While strong Brønsted acids have been used to facilitate the endothermic carbocation generation step, they significantly narrow the coexistent functional groups.² Instead of a proton, transition metals having soft Lewis acidic characters can promote the hydroalkoxylation of alkenes through the coordination of the π -Lewis acidic metal center to the carbon-carbon double bond, inducing the subsequent alcohol addition.^{3,4} However, such ionic approaches that move two electrons at once from the low HOMO of the aliphatic alkene to a proton or a metal center cannot guarantee functional group compatibility. Therefore, a completely different tactic should be developed.⁵

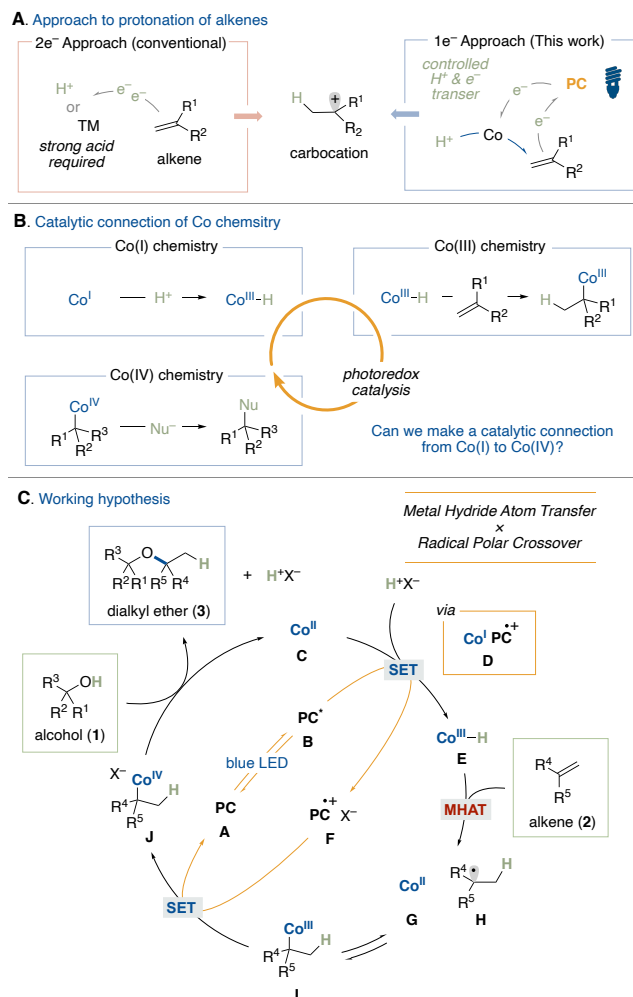
Cobalt is known to adopt a variety of valences, each having unique properties (Scheme 1B).⁶ Specifically, there are three notable features. First, a low valent Co(I) species reacts with a proton to form a Co(III) hydride species, which acts as a key intermediate in electrochemical water splitting.⁷ This process consists of a formal umpolung conversion of a proton to a hydride. Second, as exemplified by the Mukaiyama hydration reaction,⁸ Co(III) hydride undergoes metal hydride hydrogen atom transfer (MHAT) to alkenes including aliphatic ones to generate alkyl radicals and Co(II) species or alkyl Co(III). This exothermic MHAT process

allows chemists to treat alkenes as alkyl radical precursors for radical-mediated cross-coupling reactions.⁹ Therein, a catalytic generation of Co(III) hydride requires the appropriate oxidants and reductants including silanes, hantzsch esters and ascorbic acid.^{10,11} Third, an alkyl Co(IV) behaves like a carbocation, which undergoes substitution reactions with various nucleophiles.¹² A chemical or electrochemical oxidation of alkyl Co(III) accesses the corresponding alkyl Co(IV), which has been utilized to study chemical properties and reactivities.¹³ While these features have been partially incorporated into the catalytic process, they have never all been combined into a single catalytic cycle.¹⁴ Taking this into account, we questioned whether a visible light-driven photoredox catalyst would make a catalytic connection between Co(I) and Co(IV) through precise control of protons and electrons to realize strong acid-free and atom-economical Markovnikov hydroalkoxylation of alkenes (Scheme 1A, right).

We established our working hypothesis of a triple photoredox/cobalt/Brønsted acid catalysis for Markovnikov hydroalkoxylation of alkenes (Scheme 1C).^{15,16} Under visible light irradiation, photoredox catalyst **A** becomes the excited state **B** bearing high reducing ability, which undergoes a single electron transfer to Co(II) (**C**) to form a radical ion pair (**D**). Next, a weak Brønsted acid⁷ decomposes **D** into Co(III) hydride (**E**) and a radical cation of photoredox catalyst **F**. The well-known exothermic MHAT by **E** converts an alkene (**2**) to a Co(II) (**G**) and an alkyl radical (**H**), which are in equilibrium with alkylcobalt(III) (**I**). Subsequently, single electron oxidation of **I** by **F** generates an alkyl Co(IV) (**J**) with regeneration of **A**. Finally, a substitution reaction of **J** and an alcohol nucleophile (**1**) affords the desired dialkyl ether (**3**) and **C** to close the catalytic cycle. We recognized that the catalytic efficiency would be influenced by the choice of photoredox catalyst since the cycle involves two electron transfer steps: single electron reduction of Co(II) ($E_{\text{red}} = -1.31$ V vs. SCE)^{7a,17} and single electron oxidation of alkyl Co(III) ($E_{\text{ox}} = 0.39$ V vs. SCE).^{10m} To meet this condition, an appropriate photoredox catalyst bearing a high reducing ability in the excited state and moderate oxidation ability in the radical cation form is required.

According to the above-mentioned hypothesis, we found the reaction between cyclopentanol (**1a**) and 4-phenyl-1-butene (**2a**) was efficiently driven through the combination of catalytic amounts of *N*-mesityl-substituted benzo[*b*]phenothiazine (**PTH-1**), a cobalt salophen complex (**Co-1**) and collidinium triflate (**HX-1**) under visible light irradiation to produce a dialkyl ether **3aa** (Table 1, entry 1) with small amounts of benzyl ether **3aa'**¹⁷ and isomerized alkene **2a'**. In contrast to conventional protocols using

strong acids (pK_a = -2.5 for H₂SO₄ in 1,2-dichloroethane),¹⁸ our catalytic system allows us to perform the same transformation utilizing a much weaker acid **HX-1** (pK_a = 15 in MeCN).¹⁹

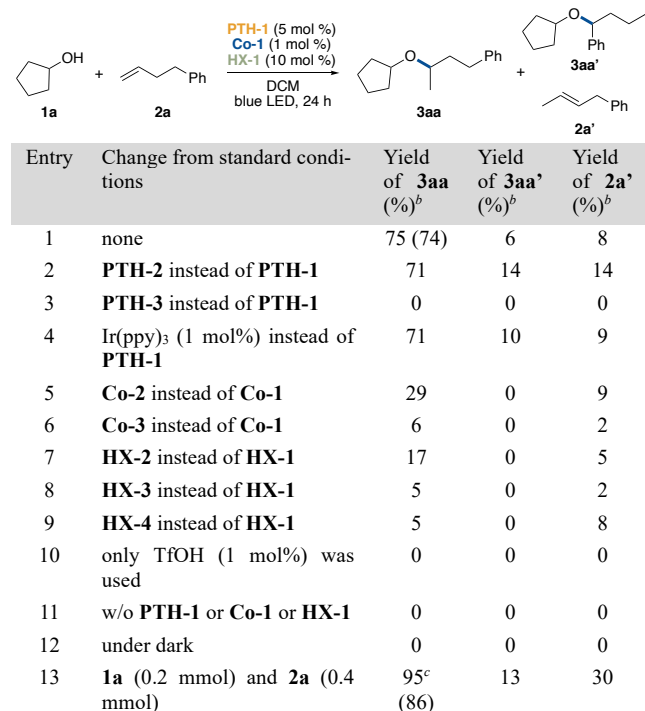


Scheme 1. Approaches to hydroalkoxylation of alkenes

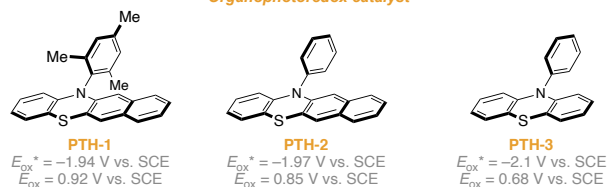
The effect of each catalyst is outlined in Table 1. The redox properties ($E_{ox}^* = -1.94$ V vs. SCE and $E_{ox} = 0.92$ V vs. SCE) of **PTH-1** satisfied the requirements for the photoredox catalyst. The benzo[*b*]phenothiazine core and a mesityl substituent of **PTH-1** were essential to secure the high reactivity (Table 1, entries 2 and 3). We assumed that the benzo[*b*]phenothiazine would guarantee high oxidation potential ($E_{ox} = 0.85$ V vs. SCE for **PTH-2** and $E_{ox} = 0.68$ V vs. SCE for **PTH-3**) and absorption in the visible region ($\lambda_{max} = 365$ nm for **PTH-2** and $\lambda_{max} = 320$ nm for **PTH-3**). The mesityl substituent slightly raised the oxidation potential and might sterically stabilize the radical cation form. Notably, Ir(ppy)₃ was found to be a potentially good catalyst (entry 4).

The cobalt Schiff complex was effective as an all-in-one cobalt catalyst covering three key functions: Co(III) hydride generation by protonation of Co(I),⁷ MHAT of alkenes by Co(III) hydride^{8–10} and nucleophilic substitution on alkyl Co(IV).¹² The structure of the cobalt Schiff complex affected the yield of **3aa**. The use of other catalysts **Co-2** and **Co-3**, which are optimal catalysts in silane-mediated protocols,¹⁰ instead of **Co-1** resulted in low conversion of **2a** (Table 1, entries 5 and 6). This might be due to the higher reduction potentials of **Co-2** ($E_{\text{red}} = -1.60$ vs. SCE)¹⁷ and **Co-3** ($E_{\text{red}} = -1.56$ vs. SCE)¹⁷ than that of **Co-1** ($E_{\text{red}} = -1.31$ V vs. SCE)^{7a,17}.

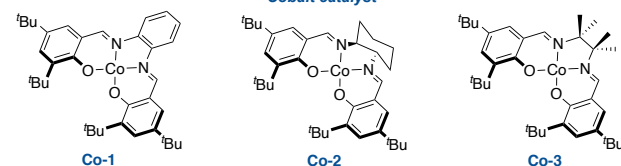
Table 1. Screening of catalysts and bases for reaction between **1a** and **2a**.^a



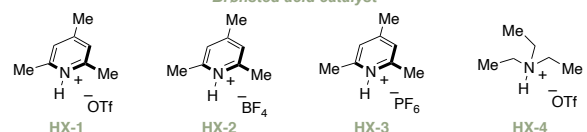
- **Organophotoredox catalyst**



- **Cobalt catalyst**



- Brønsted acid catalyst



^a Reaction was carried out with **1a** (0.6 mmol), **2a** (0.2 mmol), photoredox catalyst (0.01 mmol), Co catalyst (0.002 mmol) and Brønsted acid catalyst (0.02 mmol) in DCM (0.5 mL) under blue LED irradiation for 24 h. ^b ¹H NMR yield based on **2a**. ^c ¹H NMR yield based on **1a**.

Since the counteranion of the collidinium salt also acts as the counteranion of the phenothiazine cation radical and alkyl Co(IV), its effect on reactivity would be highly significant. Indeed, when the triflate anion was substituted with a tetrafluoroborate or a hexafluorophosphate ion, a drastic drop of product yields was observed (Table 1, entries 7 and 8). A weaker Brønsted acid, triethylammonium triflate salt, than **HX-1** was also ineffective (entry 9). To eliminate the possibility of strong acids being generated in the reaction and promoting the reaction, triflic acid was used instead of the three catalysts (entry 10).²⁰ Since the reaction did not produce the desired product at all, the transiently generated acid-promoted reaction pathway was ruled out.²¹ Control experiments revealed that the three catalysts and light irradiation were

essential to promote the reaction (entries 11 and 12). When the alcohol nucleophile was used as a limiting reagent, the product

was obtained in high yield (entry 13).

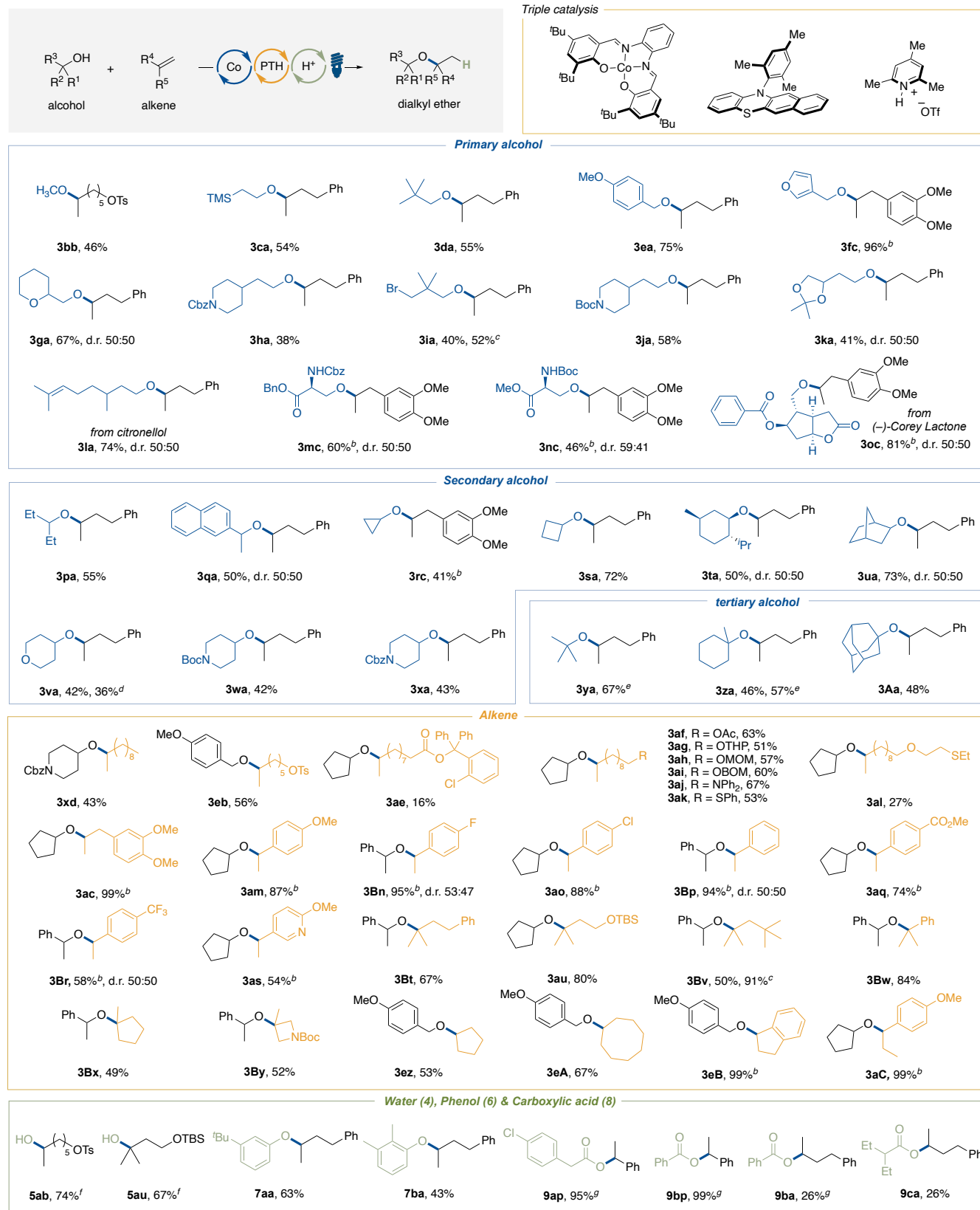


Figure 1. Substrate scope. ^a Reaction was carried out with **1**, **4**, **6** or **8** (0.6 mmol), **2** (0.2 mmol), **PTH-1** (0.01 mmol), **Co-1** (0.002 mmol) and **HX-1** (0.02 mmol) in DCM (0.5 mL) under blue LED irradiation for 24 h. ^b **1** (0.2 mmol) was used. ^c Ir(ppy)₃ (0.002 mmol) was used instead of **PTH-1**. ^d **1** (0.2 mmol) and **2** (0.4 mmol) were used. ^e **1** (2.0 mmol) was used. ^f Acetone was used instead of DCM. ^g α,α,α-Trifluorotoluene was used instead of DCM.

Next, the scope of alcohols and alkenes was investigated with the optimized reaction conditions (Figure 1). Various primary aliphatic alcohols participated in our triple catalytic hydroalkoxylation of alkenes. A simple methanol can be installed on the alkene moiety (**3bb**). Sterically encumbered substituents (**3ca** and **3da**) and a wide range of functional groups including electron-rich aromatics (**3ea** and **3fc**), tetrahydropyran (**3ga**) and benzyl carbamate (**3ha**) were tolerated. Although an alkyl halide moiety has been known to be activated by low valent cobalt species, we did not observe any decomposition (**3ia**). Acid sensitive functional groups, such as tertiary butyl carbamate and acetal, remained untouched (**3ja** and **3ka**). When citronellol was used as the alcohol nucleophile, the trisubstituted alkene of citronellol did not undergo hydroalkoxylation (**3la**). Our protocol allows for *O*-alkylation reactions of natural products and pharmaceutical drug compounds to produce the highly functionalized dialkyl ethers (**3la–3oc**).

As with primary alcohols, acyclic and cyclic secondary alcohols were competent nucleophiles to construct various dialkyl ether scaffolds (**3pa–3xa**). Notably, sterically encumbered tertiary aliphatic alcohols were applicable to this protocol (**3ya–3Aa**).

Various functional groups could be accommodated in the terminal alkene substrates (Figure 1). Representative functional groups sensitive to acid or oxidation remained untouched in the reaction conditions (**3ae–3al**). 3,4-Dimethoxy allylbenzene showed exceptionally high reactivity (**3ac**). Benzyl ethers were also synthesized by use of vinyl arenes as the alkene coupling partners (**3am–3as**).

Our protocol allowed us to treat 1,1-disubstituted aliphatic alkenes as tertiary alkylation reagents (Figure 1).²² A series of dialkyl ethers bearing bulky acyclic aliphatic chains could be prepared (**3Bt–3Bw**). Cyclic fragments including cyclopentane (**3Bx**) and azetidine (**3By**) were efficiently introduced to the product scaffold. Internal alkenes were also applicable in our protocol (**3ez–3aC**). Hydroalkoxylation of indenones or β -methyl styrene occurred with complete regioselectivities to furnish the corresponding benzyl ethers (**3eB** and **3aC**). This regioselectivity could be rationalized by the stability of alkyl radicals generated in the MHAT process (secondary benzyl radical vs. secondary aliphatic radical).

As with the conventional Markovnikov hydrofunctionalization of alkenes, this protocol tolerated other oxygen nucleophiles (Figure 1). Both 1-alkenes and 1,1-disubstituted alkenes were converted to the corresponding secondary or tertiary aliphatic alcohols in the presence of water (**5ab** and **5au**). Phenol derivatives were able to serve as nucleophiles (**7aa** and **7ba**). Both aliphatic and aromatic carboxylic acids participated in the reactions in moderate to high yields (**9ap–9ca**).²³

To gain insight on the elementary steps of the reaction mechanism, several experiments were performed. First, we focused on how Co(III)–H can be generated in the first step of our mechanistic scenario (Scheme 1C). The Stern-Volmer experiments revealed that the fluorescence of **PTH-1** is quenched by **Co-1**, but not by **HX-1** (Figures S8 and S9).¹⁷ Therefore, Co(III)–H would be generated by single electron reduction of Co(II) to Co(I) by the excited state of **PTH-1** followed by protonation of Co(I) with **HX-1**. The results of UV-Vis experiments ruled out the intermediacy of a charge transfer complex of **PTH-1** and **Co-1**.

Next, we performed a labelling experiment (Figure 2A). When methanol- d_1 **1b-D** was used as the alcohol coupling partner, a deuterium atom was incorporated into the terminal position of the alkenes. The incomplete deuteration rate indicates that the proton source was derived from **HX-1**. When methanol- d_4 was used, a CD_3 -capped dialkyl ether **3bb-D'** was obtained.

We also investigated the role of **Co-1** in the substitution step with an alcohol nucleophile (Figure 2B). **Co-1** was subjected to modified conditions of our previous reports on the decarboxylative alkylation reaction,^{15a} in which generation of an alkyl radical from a phenothiazine catalyst and a redox active ester is ensured. As with previous data, a secondary alkyl redox active ester **10a** did not afford the product. In contrast, addition of **Co-1** dramatically promoted the desired reaction to afford the ether product **11qa**. The **Co-1** complex might capture the alkyl radical to facilitate the subsequent radical polar crossover (RPC) process.

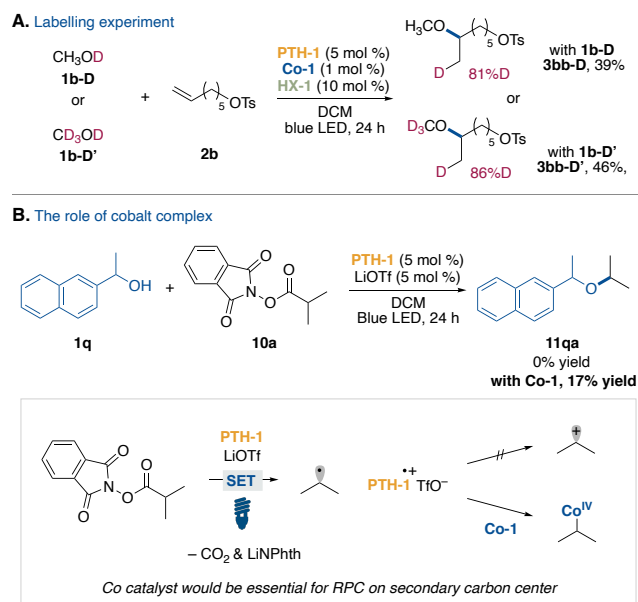


Figure 2. Substrate scope.

In summary, we have developed a visible light-driven triple photoredox/cobalt/Brønsted acid catalysis enabling Markovnikov hydroalkoxylation of alkenes. The precise control of the protons and electrons by three catalysts offers a new approach to valuable dialkyl ethers from readily available alcohols and alkenes without strong acids and external reductants/oxidants.

ASSOCIATED CONTENT

Supporting Information. Experimental details and characterization data for all new compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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catalytic connection between Co^{I} – Co^{IV}

