

A Dual Cobalt and Photoredox Catalysis for Hydrohalogenation of Alkenes

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Supporting Information Placeholder

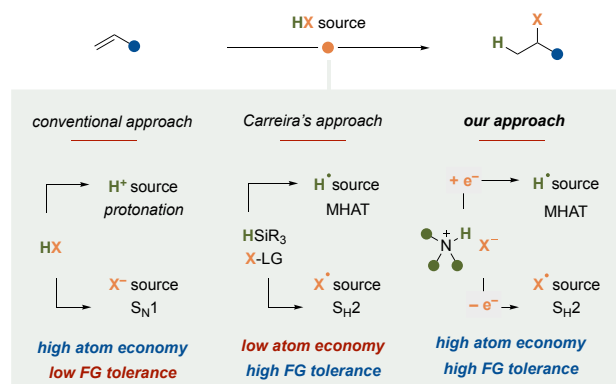
ABSTRACT: We demonstrate hydrohalogenation of aliphatic alkenes with collidine·HX salts through a dual photo-redox/cobalt catalysis. The dual catalysis enables to convert a proton and a halide anion from collidine·HX salt to a nucleophilic hydrogen radical equivalent and an electrophilic halogen radical equivalent and deliver them to an alkene moiety. This protocol allows for introduction of fluorine, chlorine, bromine or iodine atom to alkene, producing highly functionalized alkyl halides.

Alkyl halides have been classified to one of most fundamental and important organic molecules due to the high reactivity as coupling reagents and prevalent structures in natural products and pharmaceutical drugs. Therefore, synthetic methods for preparation of alkyl halides have been intensively studied. As described in textbook of organic chemistry, hydrohalogenation of alkenes using hydrogen halide (HX) is a simple, atom-economical and cost-effective process (Scheme 1A, left).^{1,2} The reaction proceeds through protonation of an alkene by HX to generate a carbocation, which reacts with a halide anion (X⁻) to forge a C–X bond. Although the protonation of aliphatic alkenes requires the strong acidity of HX (pK_a = 2.8 to 10.3 in MeCN),³ which lowered the functional group compatibility. To address this limitation, Carreira and co-workers demonstrated a radical approach for hydrochlorination of alkenes using a cobalt catalyst, hydrosilanes and tosyl chloride (Scheme 1A, middle).^{4,5} Therein, a cobalt catalyst derives a hydrogen atom from hydrosilane to alkene as a hydrogen radical through cobalt(III) hydride-mediated metal hydride hydrogen atom transfer (MHAT),⁵ resulting in formation of an alkyl radical [or alkyl cobalt(III)]. The resultant alkyl radical is captured by tosyl chloride in S_H2 manner to afford the hydrochlorination product. In addition to hydrochlorination, other halogen atoms could be also installed by choice of halogen electrophiles.⁶ Since these protocols allow to avoid the use of strong acidic HX, these protocols tolerated a broad range of functional groups. However, necessity of expensive reagents and low atom economy remained as unresolved problems.⁷

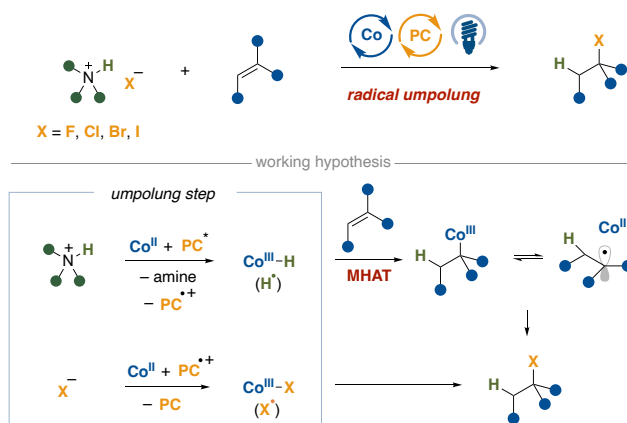
We questioned whether single electron reduction and oxidation of a proton and a halide anion from HX surrogate to a nucleophilic hydrogen radical and an electrophilic halide radical would lead to an atom-economical and high functional group compatible hydrohalogenation of alkenes (Scheme 1A, right). To accomplish this radical-based umpolung, we came up with a dual cobalt/photoredox catalysis⁸ enabling hydrohalogenation of alkenes⁹ using HX surrogate (Scheme 1B). Recently, our group¹⁰ and others¹¹ reported a cobalt(III) hydride can be generated through single electron reduction of cobalt(II) by a photoredox catalyst followed by protonation of the resultant cobalt(I). Therefore, HX surrogates bearing enough

acidity to protonate cobalt(I) is envisioned to generate a cobalt(III) hydride as a hydrogen radical source. Then, cobalt(III) hydride undergoes MHAT to aliphatic alkenes to form the corresponding alkyl cobalt(III) complex, which is in equilibrium with an alkyl radical and cobalt(II). On the other hand, a cobalt(II) becomes a cobalt(III) halide in the presence of a single electron oxidant and a halide anion, and then cobalt(III) halide would act as a halogen radical donor for alkyl radical or alkyl cobalt(III).

A. Approach to hydrohalogenation of alkenes



B. A dual cobalt/photoredox catalysis for hydrohalogenation of alkenes



Scheme 1. Approaches for hydrohalogenation of alkenes

Based on the previous our reports, we began our investigation of hydrobromination of aliphatic alkenes using a photoredox catalyst, a cobalt catalyst and HBr surrogate. Then, we found that the desired hydrobromination of 4-phenyl-1-butene (**1a**) was promoted by use of a collidine·HBr salt (**2a**) and catalytic amount of Ir(ppy)₃ and

Co-1 to afford the desired adduct **3aa** in 71% isolated yield (Table 1, entry 1). **2a** was easily synthesized from hydrogen bromide and collidine.

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

Entry	Change from standard conditions	Yield of 3aa (%) ^b
1	none	>99 (71) ^c
2	2b instead of 2a	0
3	2c instead of 2a	0
4	2d instead of 2a	0
5	Co-2 instead of Co-1	96
6	Co-3 instead of Co-1	94
7	PTH instead of Ir(ppy)3	31
8	Mes-Acr instead of Ir(ppy)3	0
9	4CzIPN instead of Ir(ppy)3	0
10	w/o Ir(ppy)3 or Co-1	0
11	under dark	0

HBr surrogate (pKa in MeCN)			
 2a (pKa = 15.0)	 2b (pKa = 12.5)	 2c (pKa = 18.83)	 2d (pKa = 24.31)

cobalt catalyst		
 Co-1	 Co-2	 Co-3

photoredox catalyst		
 Ir(ppy)3	 PTH	 Mes-Acr Me ⁺ ClO ₄ ⁻
		 4CzIPN

^a Reaction was carried out with **1a** (0.2 mmol), **2a** (0.2 mmol), photoredox catalyst (0.002 mmol) and Co catalyst (0.002 mmol) in THF (1.0 mL) under blue LED irradiation for 15 h. ^b ¹H NMR yield based on **1a**. ^c isolated yield.

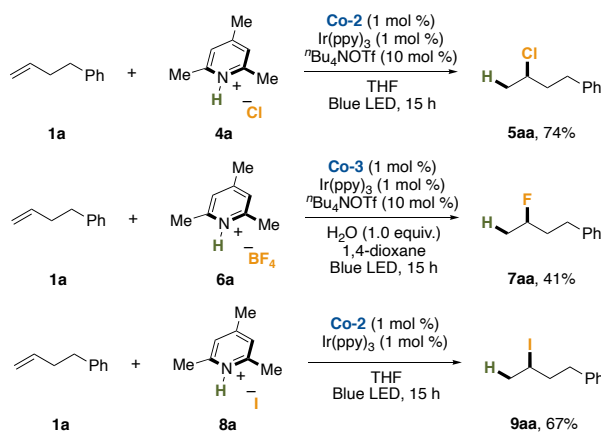
Since trialkylammonium or anilinium salts have been utilized as a mild Brønsted acid in protonation of cobalt(I),¹² various base·HBr salts were mainly evaluated as HBr surrogates. Then, we found that **2a** exclusively promoted the reaction (Table 1, entries 2–4). When a pyridine·HBr (**2b**) (pKa = 12.5 in MeCN) was used instead of **2a** (pKa = 15.0 in MeCN)¹³, hydrobromination product was not obtained at all (entry 2).¹⁴ Other ammonium salts triethylamine·HBr **2c** (pKa = 18.83 in MeCN)¹⁰ and 1,8-diazabicyclo[5.4.0]-7-undecene·HBr **2d** (pKa = 24.31 in MeCN)¹³ bearing higher pKa than **2a** were not effective due to the insufficient acidity for protonation of

cobalt(I) species (entries 3 and 4). On the other hands, the reaction efficiency was not affected by structure of cobalt catalysts. For examples, **Co-2** and **Co-3** containing 1,1,2,2-tetramethylethylene diamine and phenylene diamine scaffolds could be used as comparable catalysts (entries 5 and 6). Expectedly, the choice of photoredox catalysts was also key factor in this reaction because the photoredox catalyst needs to reduce cobalt(II) [$E_{\text{red}}(\text{Co-1}) = -1.60$ V vs. SCE] and oxidize cobalt(II) [$E_{\text{ox}}(\text{Co-1}) = 0.00$ V vs. Fc^+/Fc] or a bromide anion [$E_{\text{ox}} = 0.80$ V vs. SCE]. $\text{Ir}(\text{ppy})_3$ has sufficient potentials for these redox events. Although **PTH** bearing comparable redox potentials with $\text{Ir}(\text{ppy})_3$ showed moderate catalytic activity, **Mes-Acr** and **4CzIPN** were not suitable due to the inconsistent redox potentials (entries 7–9). Further optimization data is provided in Supporting Information. Control experiments revealed that a photoredox catalyst, a cobalt catalyst and light are essentials to promote the reaction (entries 10 and 11).

With these optimal conditions in hands, we turned our attention to other hydrohalogenation of alkenes. Although some modifications on the reaction conditions were required, hydrochlorination, hydrofluorination and hydroiodination were also achieved by use of collidine·HCl (**4a**), collidine·HBF₄ (**6a**)¹⁵ and collidine·HI (**8a**), that are easily prepared by corresponding acids (Figure 1A). To see the robustness and synthetic utility of this protocol, scope of alkenes was investigated (Figure 1B). Terminal alkene substrates (**1b** and **1c**) having acid-sensitive ester and methoxymethyl groups were converted to alkyl halides without loss of such functional groups. The hydrofluorination of **1c** does not proceed at all, and γ -valerolactone was obtained.¹⁶ Our protocol allows to synthesize tertiary alkyl halides from 1,1-disubstituted alkenes (**1d–1g**). Acyclic/cyclic structures and various functional groups were tolerated. Isopropenyl boronate (**1h**) could be converted to α -haloboronate derivative, which is one of valuable synthetic intermediates.¹⁷ Aromatic (**1i**) and electron-deficient (**1j**) alkenes were converted to reactive alkyl halides, but the products were hard to be isolated. Notably, this protocol allows to use cyclic and acyclic internal alkenes (**1k** and **1l**) as alkene substrates, providing sterically encumbered secondary and tertiary alkyl halides. The hydrofluorination with these substrates resulted in inefficient product formation. The high functional group compatibility was ensured by success of functionalization of natural products and pharmaceutical drug derivatives, such as allylglycine, rotenone, indomethacin and oxapropzin (**1m–1p**). When the reactions with **1a**, **1b** and **1g** were tested with use of hydrogen bromide instead of **2a**, respectively, only **3aa** was obtained.

Subsequently, we turned our attention to explore the reaction pathway. There are two conceivable mechanisms on C–X bond formation step. The first one is S_H2 reaction between an alkyl radical or an alkyl cobalt(III) and a cobalt(III) halide¹⁸ as described in Scheme 1B.¹⁹ The second one is S_N2 reaction between an halide anion and an alkyl cobalt(IV) species.²⁰ To distinguish the reaction mechanisms, several experiments were conducted. First, the reaction using 4-penten-1-ol derivative **1q** and each collidine·HX salt was carried out under the optimal conditions (Figure 2A). When **2a** was used, hydrobromination product **3qa** was obtained along with hydroalkoxylation product **10q**.²¹ The formation of **10q** implied the intermediacy of a carbocation or an alkyl cobalt(IV) complex. While the reaction with **4a** afforded **5qa** over **10q**, the reaction with **6a** gave only **10q**. This result indicated hydrofluorination reaction would proceed through single electron oxidation of alkyl cobalt(III) to alkyl cobalt(IV), which reacts with a fluoride anion from tetrafluoroborate in S_N2 manner. It is assumed that the differences in reactivity between hydrobromination/hydrochlorination and hydrofluorination observed in Figure 1B are attributed to variations in reaction pathways.

A. Application to hydrochlorination and hydrofluorination



B. Substrate scope

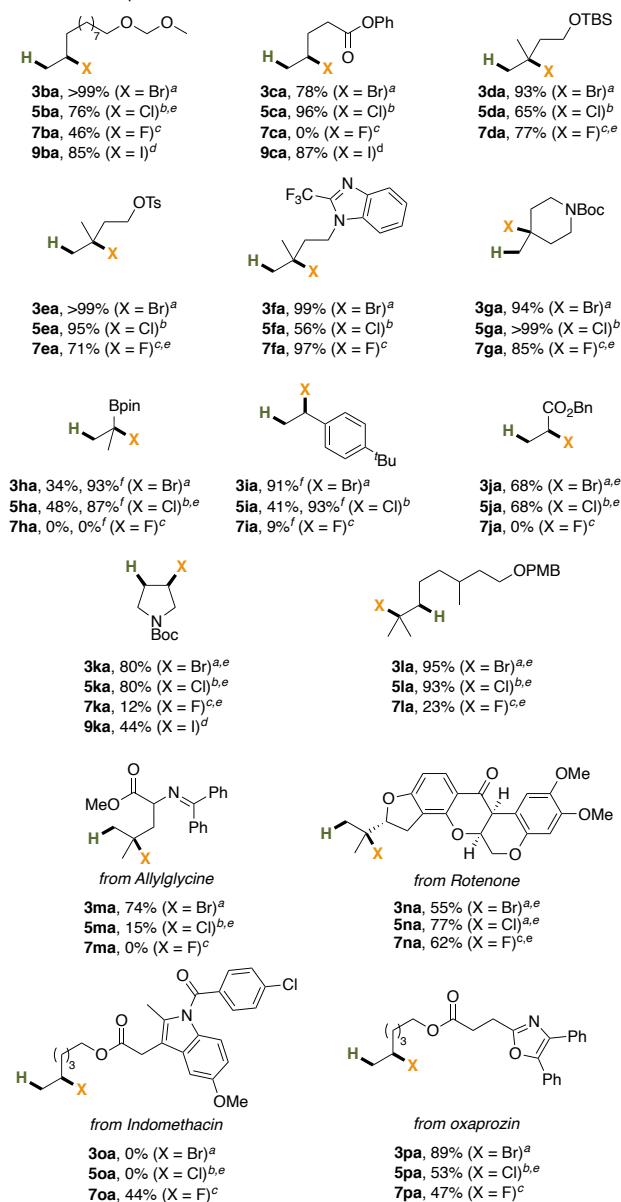
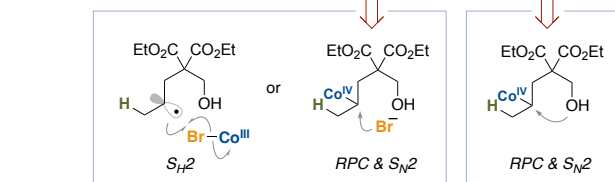
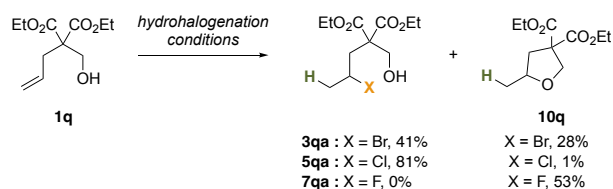


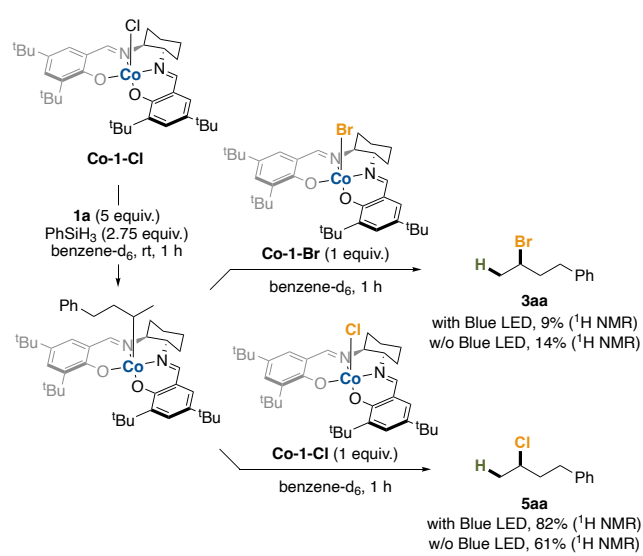
Figure 1. Substrate scope. ^a Reaction was carried out with **2a** (0.2 mmol), **1** (0.2 mmol), **Co-1** (0.002 mmol) and Ir(ppy)₃ (0.002 mmol) in tetrahydrofuran (1.0 mL) under blue LED irradiation for 15 h. ^b Reaction was carried out with **4a** (0.2 mmol), **1** (0.2 mmol), **Co-2** (0.002 mmol), tetrabutylammonium triflate (0.02 mmol) and Ir(ppy)₃ (0.002 mmol) in tetrahydrofuran (1.0

mL) under blue LED irradiation for 15 h. ^c Reaction was carried out with **6a** (0.6 mmol), **1** (0.2 mmol), **Co-3** (0.002 mmol), tetrabutylammonium triflate (0.02 mmol), H₂O (0.2 mmol) and Ir(ppy)₃ (0.002 mmol) in 1,4-dioxane (1.0 mL) under blue LED irradiation for 15 h. ^d Reaction was carried out with **8a** (0.2 mmol), **1** (0.2 mmol), **Co-2** (0.002 mmol) and Ir(ppy)₃ (0.002 mmol) in tetrahydrofuran (1.0 mL) under blue LED irradiation for 15 h. ^e The reaction conditions were slightly modified (See Supporting Information). ^f ¹H NMR yield.

A. Distinguishment of RPC-S_N2 vs. S_H2 Pathway



B. Stoichiometric reactions between alkyl Co(III) complex and Co(III) halide complex



C. Stoichiometric reactions between alkyl radical and Co(III) halide complex

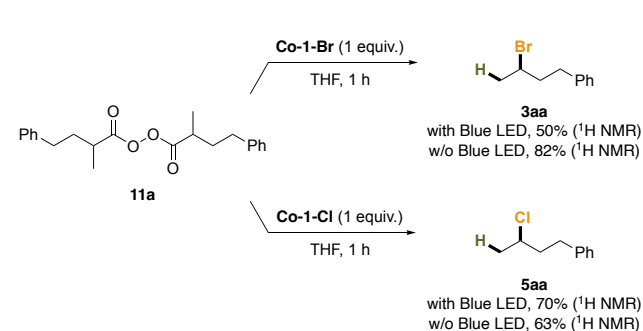


Figure 2. Mechanistic studies.

To gain further mechanistic information, we tested the stoichiometric reactions between *in situ* generated alkyl cobalt(III) and an isolated cobalt(III) bromide or cobalt(III) chloride (Figure 2B). According to the reported procedures,²² an alkyl cobalt(III)

was prepared through the reaction between **1a** and a cobalt(III) chloride salen complex (**Co-1-Cl**) in the presence of phenylsilane. The obtained alkyl cobalt(III) complex was subjected to the reaction with an isolated cobalt(III) bromide salen complex (**Co-1-Br**). With or without a light irradiation, the desired alkyl bromide **3aa** was afforded. When the reaction was carried out with **Co-1-Cl** instead of **Co-1-Br**, the corresponding alkyl chloride **5aa** was obtained. Another stoichiometric reactions between diacyl peroxide (**11a**) and **Co-1-Br** or **Co-1-Cl** were carried out (Figure 2C). With or without a light irradiation, both reactions proceeded well to form **3aa** and **5aa** in high yields, respectively. In these reactions, diacyl peroxide decomposed to the corresponding a secondary alkyl radical after homolytic cleavage of O–O bond²³ and decarboxylation and the resultant radical reacts with a cobalt halide complex in S_H2 manner. These results supported the intervention of S_H2 pathway on hydrobromination reaction and hydrochlorination. Since there were no significant differences in product yield with or without light (Figures 2B and 2C), we concluded that key C–X bond formation is not affected by light.

In summary, we demonstrated the dual photoredox/cobalt-catalyzed hydrogenation of aliphatic alkenes with collidine·HX salts. The dual catalysis enables to convert a proton and a halide anion to a nucleophilic hydrogen radical and an electrophilic halogen radical, installing them onto alkene moiety. This radical-based umpolung strategy ensures high atom economy and broad functional group tolerance, that could not be achieved by the reported methods. Thus, this protocol allows us to access densely functionalized alkyl halides. Now, application of this strategy to other functionalizations is ongoing in our laboratory.

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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