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Visible-light-mediated conversion of alcohols to halides

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The development of new means of activating molecules and bonds for chemical reactions is a fundamental objective for chemists. In this regard, visible-light photoredox catalysis has emerged as a powerful technique for chemoselective activation of chemical bonds under mild reaction conditions. Here, we report a visible-light-mediated photocatalytic alcohol activation, which we use to convert alcohols to the corresponding bromides and iodides in good yields, with exceptional functional group tolerance. In this fundamentally useful reaction, the design and operation of the process is simple, the reaction is highly efficient, and the formation of stoichiometric waste products is minimized.

Visible-light sensitization is an attractive means to initiate organic reactions[1,2] because of the lack of absorbance of visible light by organic compounds. This means that the side reactions often associated with the use of high-energy UV light are minimized[3,4]. Photocatalysts such as $Ru(bpy)_3Cl_2$ (bpy = 2,2′-bipyridine) offer a means to selectively functionalize organic molecules; however, their use in initiating chemical reactions relevant to organic chemistry has been, until recently, very limited[5]. In 2008, work on asymmetric aldehyde alkylations (MacMillan)[6] and formal [2 + 2] cycloaddition reactions (Yoon)[7] demonstrated that visible-light photoredox catalysis was capable of initiating powerful transformations in organic synthesis. The development of new ways of activating molecules for chemical reactions is a fundamental objective in chemistry, both for target-oriented[8] and method-driven[9,10] purposes. In particular, the development of new methods in catalysis has brought to light new reactivity and/or selectivity for synthetic transformations[11–15]. These selective processes enable the synthesis of complex molecules without the necessity for protective groups[16] or unnecessary redox manipulations[17,18]. Visible-light photoredox catalysis represents another mode of selectively activating organic molecules towards chemical transformations, and it has recently been shown to be applicable to a variety of complex synthetic reactions[19–25]. We have been particularly interested in using photoredox catalysis as a new means to activate carbon–halogen and carbon–hydrogen bonds via the reductive quenching pathway available to photoredox catalysts.

The transformation of alcohols to the corresponding halides is one of the most widely used reactions in organic synthesis. Several methods are available, making use of various stoichiometric reagents including thionyl chloride[26], phosphorous halides[27,28], phenylmethyleniminium[29], benzoxazolium[30], Vilsmeier–Haack reagents[31], Viehe's salts[32] and cyclopropenium ions[33]. However, these methods often require advanced preparation of the reagents or harsh conditions. The mildest of these transformations, the Appel reaction, uses PPh_3 in combination with an electrophilic halogen source such as CCl_4, CBr_4 or I_2. Furthermore, triphenylphosphine, and related compounds, are among the most ubiquitous reagents in organic synthesis, functioning as two-electron reductants in the Mitsunobu, Wittig and Staudinger reactions, and in the conversion of alcohols to halides. It is also one of the least atom-economical reagents[34], often affecting just a single atom replacement during the course of a reaction. In addition, the stoichiometric waste by-product triphenylphosphine oxide is often difficult to remove from the reaction mixture. Supported phosphine reagents can be used to alleviate the purification issue[35]; however, these reactions still generate stoichiometric waste by-products. Given the wide variety of reactions that can be accessed using these reagents, the innovation of catalytic methods is a primary goal for the development of environmentally friendly chemical approaches for the nucleophilic substitution of alcohols[36].

In this Article, we report a mild and operationally simple method for the transformation of alcohols to the corresponding bromides and iodides using 1.0 mol% of a visible-light-activated photocatalyst. Specifically, with respect to both reaction efficiency and subsequent reaction purification, the minimization of stoichiometric chemical waste makes this method an industrially viable and green alternative to the existing methodologies (Fig. 1).

Exploring new reactivity concepts in the area of photoredox catalysis is an integral part of our ongoing research endeavours. Recently, we have demonstrated the reductive dehalogenation of activated C–X bonds using the visible-light-activated photoredox catalyst $Ru(bpy)_3Cl_2$. We further expanded the scope of photoredox catalysis in C–C bond-forming reactions via intra- and intermolecular radical addition onto indoles, pyrroles and olefins[22–24] and oxidative aza-Henry reaction of tetrahydroisoquinolines[25]. All of these transformations proceed through the reductive quenching of the excited catalyst $[Ru(bpy)_3{}^{2+\star}$ or $Ir(ppy)_2(dtbbpy)^{+\star}]$ and rely upon the strong reducing properties of $Ru(bpy)_3{}^+$ or $Ir(ppy)_2(dtbbpy)$ [ppy = 2-phenylpyridine; dtbbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine]. Although oxidative quenching of $Ru(bpy)_3{}^{2+\star}$ provides the strong oxidant $Ru(bpy)_3{}^{3+}$ (1.27 V vs. saturated calomel electrode [SCE])[5], it has found very limited application in organic synthesis[37–39]. This deficiency has also been noted in a recent communication by the Yoon group detailing the intramolecular [2 + 2] cycloaddition of electron-rich styrenes using the oxidative quenching cycle[40]. Recent research has shown that reduction of tetrahalomethanes (CCl_4 and CBr_4) in dimethylformamide (DMF) using super stoichiometric quantities of Fe and Cu powder can convert alcohols into the corresponding halides via a Vilsmeier–Haack type reagent (Fig. 1)[41]. We therefore envisioned that catalytic generation of Vilsmeier–Haack reagents could be achieved under mild conditions through the oxidative quenching of $Ru(bpy)_3{}^{2+\star}$ with polyhalomethanes CBr_4 ($E_{1/2} = -0.30$ V vs. SCE)[42] or CHI_3 ($E_{1/2} = -0.49$ V vs. SCE)[42] in DMF, which

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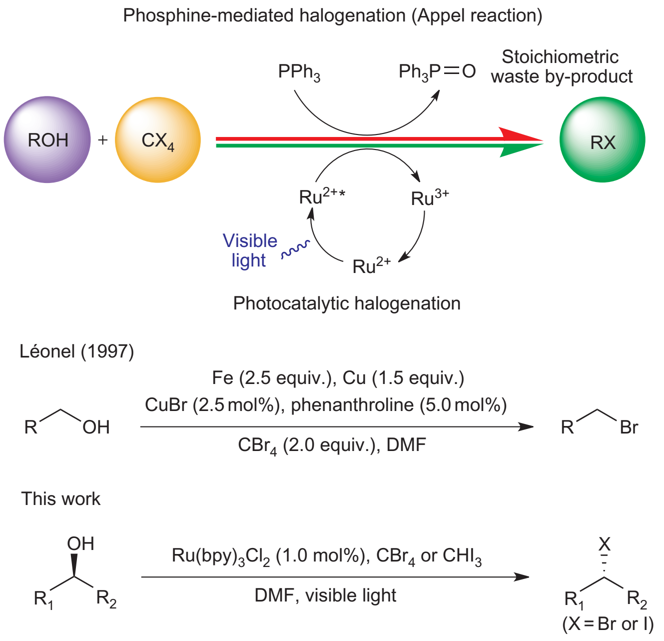


Figure 1 | Phosphine-free halogenation of alcohols using visible-light photoredox catalysis. Design of a catalytic Appel reaction using visible-light photoredox catalysis. Encouraging literature was authored by Léonel and coworkers on the stoichiometric metal-mediated reduction of polyhalomethanes for the generation of alkyl halides from alcohols. The photoredox catalyst, Ru(bpy)$_3$Cl$_2$ replaces stoichiometric Ph$_3$P in the halogenation reaction. DMF = *N,N*-dimethylformamide.

eventually serves to activate the alcohol for a nucleophilic substitution reaction. In this case, substitution by a nucleophilic halide would provide a phosphine-free halogenation of alcohols using commercially available and easily handled reagents, which can be manipulated on the bench without the need for specialized equipment.

Results

To test our hypothesis, we used carbon tetrabromide as both the halogen source and oxidative quencher in the photocatalytic cycle. We were delighted to find that visible-light irradiation (blue light-emitting diode (LED), $\lambda_{max} = 435$ nm) of alcohol **1a** (0.5 mmol) and CBr$_4$ (2.0 equiv.) in DMF in the presence of Ru(bpy)$_3$Cl$_2$ (1.0 mol%) at 25 °C for 5 h furnished the corresponding bromide **2a** in 70% isolated yield. Further optimization of the reaction found that the addition of an external halide source, such as NaBr (2.0 equiv.), improved the yield to 90% (Fig. 2).

However, a solvent screen, including CH$_3$CN, tetrahydrofuran (THF) and CH$_2$Cl$_2$, failed to afford the desired product in any appreciable yield. Meanwhile, control reactions also showed that rigorous exclusion of light or the absence of Ru(bpy)$_3$Cl$_2$ failed to produce any bromide product at room temperature. Low reactivity (<20% conversion) was observed without Ru(bpy)$_3$Cl$_2$ only if the reaction was heated at 80 °C for 12 h, presumably due to the liberation of HBr. These results support the necessity of the photoredox catalyst in the observed halogenation reaction.

The scope of the reaction under optimized conditions was explored using a set of alcohols (Table 1). Primary alcohols (entries 1–11) were smoothly transformed to their corresponding bromides with 77–98% yields. The reaction is highlighted by outstanding functional group tolerance and can be carried out in the presence of ethers (entries 1–3), silyl ethers (entry 11), alkenes (entries 3–5), alkynes (entry 9), carbamates (entries 5–8), esters (entries 6, 12) and phenols (entry 10). Acyclic, secondary alcohols were also viable substrates for the bromination reaction (entries 12 and 13), although the reaction rate was attenuated compared to primary alcohols. Interestingly, the use of cyclic secondary alcohol **1o** resulted in the isolation of formate ester **4o** as the sole product, even after a prolonged reaction time (24 h), providing information on potential reactive intermediates produced during the course of the reaction (*vide infra*).

With the success of the bromination of alcohols, we next focused on the complementary iodination reaction. To achieve iodination, we simply changed the halogen source from carbon tetrabromide to iodoform. Transformation of alcohols (entries 15–20) to their corresponding iodides was achieved in similar yields as for bromination. As well as the good yields and wide scope of this process, functional group tolerance was also remarkable. As presented in Table 1, alkynes, alkenes (including sensitive *cis*-allylic alcohols), acid-sensitive trisubstituted alkenes, electron-rich aromatics, carbamates, sulfonamides and esters were not affected under the conditions. Acid-sensitive functional groups such as *tert*-butyl carbamates and silyl ethers were also tolerated if 2,6-lutidine was added. The success of the reaction in the presence of these acid-labile protective groups makes this method very attractive and competitive with known methods for the transformation of alcohols to halides. Furthermore, it is also noteworthy that the halogenations can be conducted on gram scales. In this case, tetrabutylammonium bromide was used instead of sodium bromide to improve the solubility in DMF. The bromination of alcohol **1c** produced bromide **2c** in nearly identical yield compared with discovery-scale experiments, further demonstrating the efficiency of the Ru(bpy)$_3$Cl$_2$/CBr$_4$ photocatalytic system.

Mechanistic investigation and discussion

A key piece of mechanistic evidence was obtained from the observed formate ester product **4o** (Table 1, entry 14). Indeed, premature quenching of the reaction of primary alcohols also led to the isolation of formate ester by-products. To delineate the source of the formate ester, we subjected alcohol **1f** to the bromination conditions in DMF-*d*$_7$ and stopped the reaction after 4 h (Fig. 3a). Together with the unconsumed starting material, the reaction provided a mixture of bromide **2f** and formate ester **4f**, with 100% deuterium incorporation. This result indicates that DMF is involved in this photocatalytic transformation, and the reactive intermediate generated may be an iminium species derived from the reaction of the alcohol with an *in situ* generated Vilsmeier–Haack reagent. Furthermore, the prolonged reaction times required for secondary alcohols in comparison to primary alcohols suggest that the reaction proceeds via an S$_N$2 pathway. This hypothesis was also supported by the isolation of formate ester **4o**, and none of the desired bromide, when **1o** was exposed to the same reaction conditions. The increased steric demand of the cyclic alcohols appears to preclude the S$_N$2 pathway.

Léonel has proposed a carbene mechanism, consistent with their data, to account for the halogenation of alcohols using the Fe/Cu/CBr$_4$ system[43]. However, evidence collected to date for photoredox reactions related to the chemistry in this paper are consistent with single-electron processes and the corresponding radical reactions. Indeed, we have found that CBr$_4$ quenches the Ru(bpy)$_3^{2+}$ excited state, as indicated by luminescence quenching experiments (Stern–Volmer constant, $K_{SV} = 14.4\ M^{-1}$), to provide the

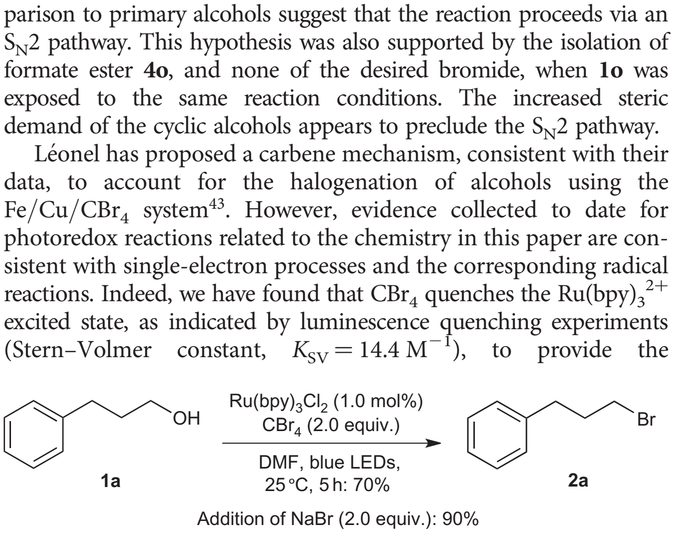
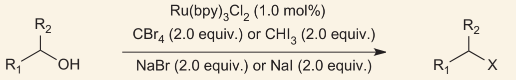
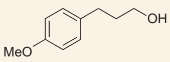
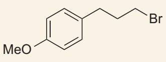
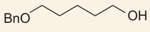
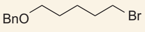
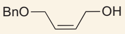
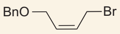
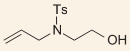
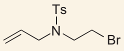
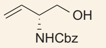
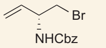
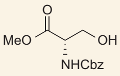
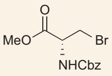
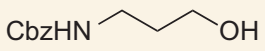
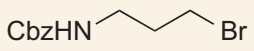
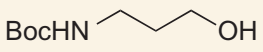
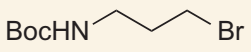
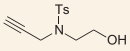
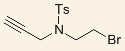
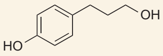
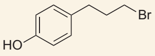
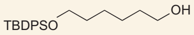
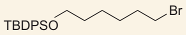
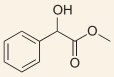
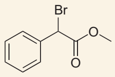
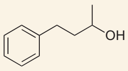
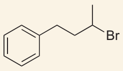
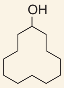
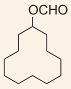
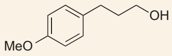
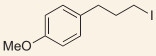
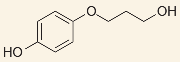
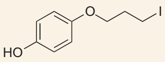
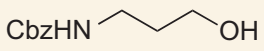
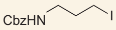
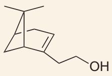
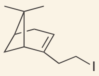
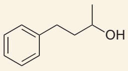
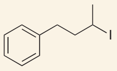
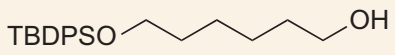
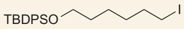


Figure 2 | Ru(bpy)$_3$Cl$_2$ catalysed bromination of alcohol 1a. The reaction afforded bromide product **2a** in 70% yield without an external halide source. With the addition of 2.0 equiv. NaBr, the yield was improved to 90%.

Table 1 | Conversion of alcohols 1 to bromides 2 or iodides 3 using photoredox catalysis.



1 → **2** (X = Br) or **3** (X = I)

Entry	Substrate	Product	Yield (%)*
		Bromination Examples	
1	 **1b**	 **2b**	90
2	 **1c**	 **2c**	98 (96)†
3	 **1d**	 **2d**	78
4	 **1e**	 **2e**	77
5	 **1f**	 **2f**	83
6	 **1g**	 **2g**	81
7	 **1h**	 **2h**	96
8	 **1i**	 **2i**	75‡
9	 **1j**	 **2j**	86
10	 **1k**	 **2k**	84
11	 **1l**	 **2l**	86‡
12	 **1m**	 **2m**	86
13	 **1n**	 **2n**	75
14	 **1o**	 **4o**	92§
		Iodination Examples	
15	 **1b**	 **3b**	91
16	 **1p**	 **3p**	86
17	 **1h**	 **3h**	91
18	 **1q**	 **3q**	65
19	 **1n**	 **3n**	72
20	 **1l**	 **3l**	78‡

*Isolated yield after purification by chromatography on SiO_2; †The reaction was performed on a 5 mmol scale, 14% of starting material was recovered; ‡2,6-lutidine (3.0 equiv.) was added to buffer HX (X = Br, I) that was produced; §No bromide product was observed.

tribromomethyl radical. To distinguish between the radical pathway and a potential carbene mechanism, we conducted additional experiments using radical traps (such as α-methylstyrene) as substrates with $Ru(bpy)_3Cl_2$ (1.0 mol%) and CBr_4 (2.0 equiv.) in both DMF and CH_3CN (Fig. 3b). In CH_3CN, the Fe/Cu-mediated reaction reported by Léonel provides only the corresponding dibromocyclopropane product, consistent with the generation of dibromocarbene. However, using $Ru(bpy)_3Cl_2$, dibromocyclopropane product **6** was not observed in either solvent after 12 h. Instead, compound **5b** was the only product observed, a consequence of the addition of tribromomethyl radical to styrene to generate **5a** followed by oxidation (by Ru^{3+} or CBr_4) then

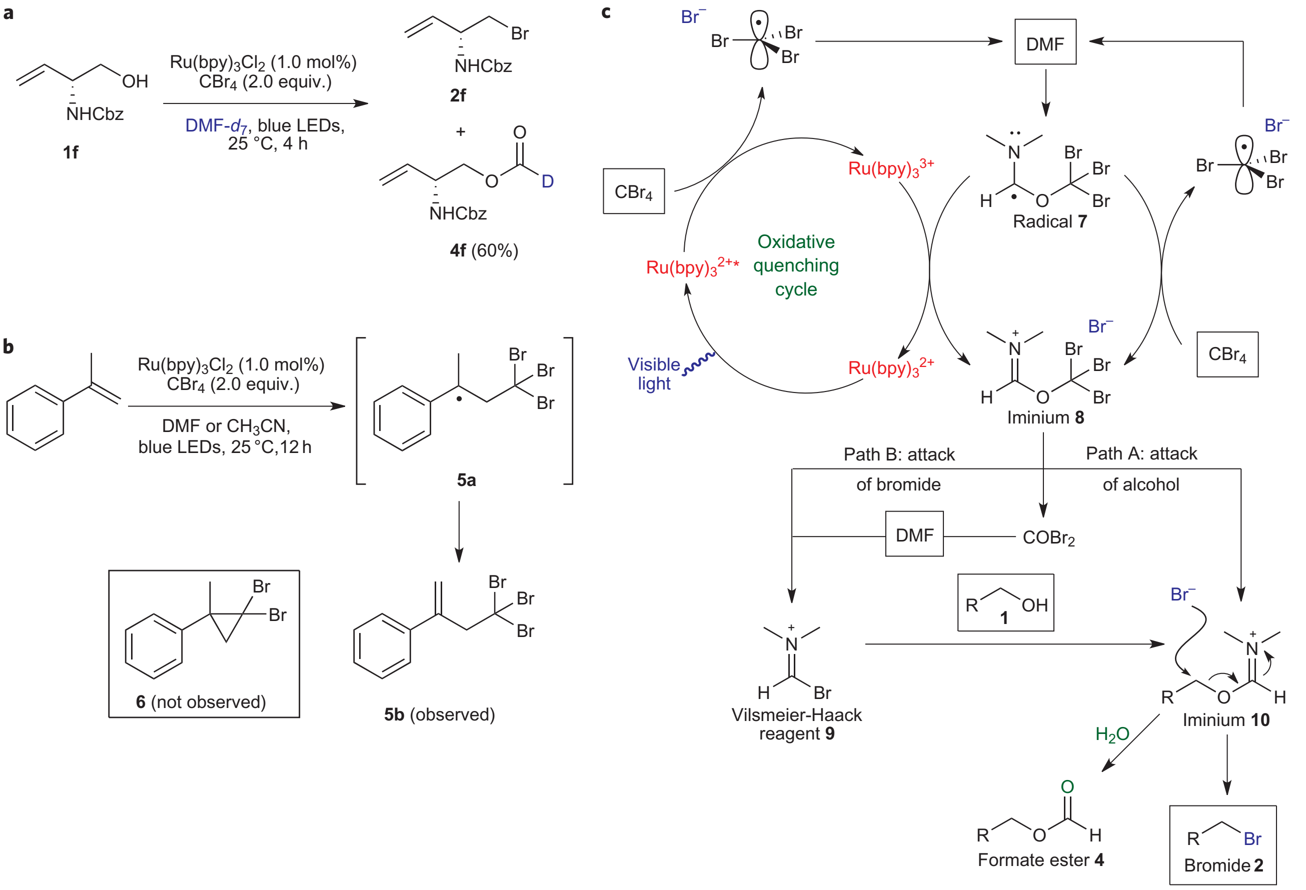


Figure 3 | Mechanistic investigation of the photocatalytic halogenation. a, 100% deuterium incorporation in **4f** indicates that DMF is involved in the transformation, and the reactive intermediate may be an iminium species derived from the reaction of alcohol with a Vilsmeier–Haack type reagent. **b**, Trapping of the reactive species with α-methylstyrene (in both DMF and CH_3CN) led to product **5b**, indicating that the reaction is proceeding via a radical pathway, but the lack of observation of product **6** ruled out the possibility of the carbene pathway using photocatalysis, in contrast to the Fe/Cu halogenation system of Léonel. **c**, A plausible mechanism is proposed, starting with the oxidative quenching of $Ru(bpy)_3^{2+}$ by CBr_4 to give $^{\bullet}CBr_3$, which combines with DMF to form intermediate **7**. Oxidation by $Ru(bpy)_3^{3+}$ or CBr_4 gives the Vilsmeier–Haack type reagent, which reacts with alcohol **1** followed by nucleophilic displacement to give bromide product **2**, or upon premature aqueous workup to give formate ester **4**.

elimination. These results support a mechanism of single-electron reduction of CBr_4 using photocatalyst $Ru(bpy)_3Cl_2$ to initiate the halogenation reaction. With respect to these results and our luminescence quenching experiments, we propose a mechanism in which the single-electron reduction of CBr_4 by $Ru(bpy)_3^{2+*}$ forms $Ru(bpy)_3^{3+}$ and $^{\bullet}CBr_3$. Trapping of the electron-deficient radical by DMF generates a highly stabilized radical **7**, which can be oxidized by $Ru(bpy)_3^{3+}$ (1.27 V vs. SCE) to form the iminium intermediate **8**, regenerating the photocatalyst $Ru(bpy)_3^{2+}$. Alternatively, **7** can be oxidized by reaction with another molecule of CBr_4 as observed in atom-transfer radical chain reactions[44]. At this stage, two reasonable pathways may be considered for the formation of product **2**. The first proceeds with direct addition of alcohol **1** to iminium **8** to form intermediate **10**, which can undergo S_N2 displacement by bromide to provide the final product (path A). In the second pathway, addition of the bromide ion to **8** produces the Vilsmeier–Haack reagent **9**, which reacts with alcohol **1** to afford the intermediate **10** (path B). In addition, $COBr_2$ is generated as a by-product in both pathways, and it has been shown to react with DMF to produce **9** with liberation of CO_2 (ref. 45), funnelling both of the reaction pathways to the common intermediate **10**, which upon premature quenching with water can provide the observed formate ester by-product **4** (Fig. 3c).

Although the data up to this point were consistent with an S_N2 displacement of the activated iminium ester, treatment of the optically pure alcohol **11** (99% e.e.) under the optimized reaction conditions provided bromide **12** as a racemic mixture, provoking a reevaluation of our mechanistic interpretation of this transformation (Fig. 4a). However, the analysis of isolated bromide **12**, after only 35% conversion of **11**, indicated that a stereospecific displacement was occurring, as **12** was found to be still highly optically enriched (90% e.e.). This result provided further evidence against a solvolysis mechanism. To further satisfy our hypothesis that an S_N1 mechanism was not viable, chiral HPLC analysis (Chiralcel OD, 5% hexanes/isopropanol) of the formate ester **13** (after saponification with K_2CO_3 in MeOH) confirmed that racemization was also not occurring at the stage of our proposed reactive iminium intermediate. In other words, solvolysis or degenerate displacement of the activated intermediate by DMF was not occurring. On the basis of these observations, the activated intermediate appears to be configurationally stable and racemization can be attributed to the S_N2 displacement of bromide in **12** with NaBr (ref. 45). This displacement and subsequent racemization is observed in the time-dependent loss of optical activity during the subjection of optically enriched **12** (99% e.e.) to the reaction conditions (Fig. 4b).

Conclusions

We have developed a catalytic, phosphine-free method for the bromination and iodination of alcohols using visible-light

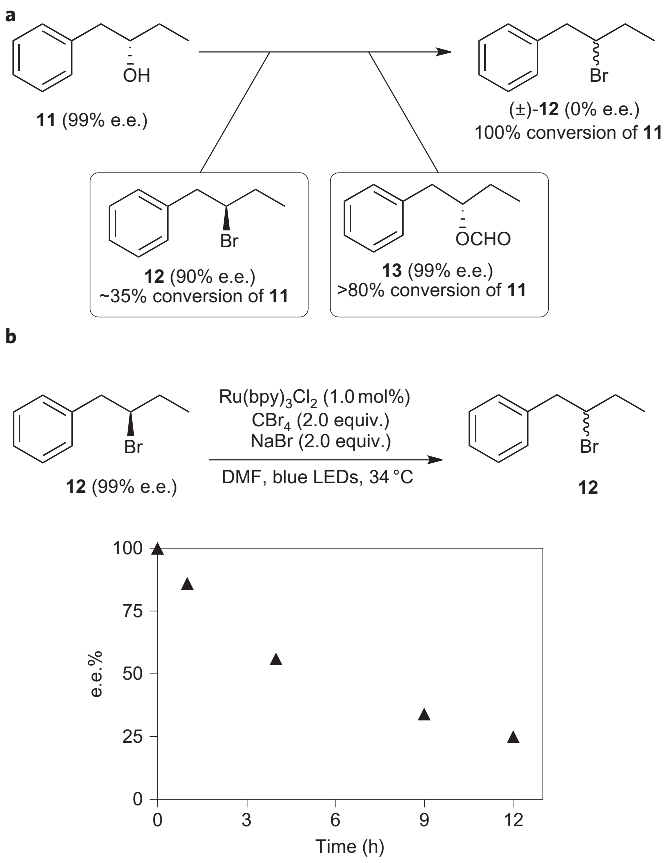


Figure 4 | Degenerate S_N2 reaction results in racemization with optically enriched alcohol 11. a, Racemic bromide product **12** was obtained when optically pure alcohol **11** was treated with $Ru(bpy)_3Cl_2$ (1.0 mol%), CBr_4 (2.0 equiv.) and NaBr (2.0 equiv.) in DMF for 12 h. However, highly optically enriched bromide **12** was isolated at low conversion of **11**, which indicates that the racemization may be due to a concomitant Finkelstein reaction. This hypothesis was confirmed by the isolation of chiral formate ester **13** at high conversion of **11** indicating the reactive intermediate is configurationally stable. **b**, Time-dependent loss of optical activity of chiral bromide **12** implies that the racemization is due to a degenerate S_N2 reaction.

photocatalysis. The reaction is highlighted by its exceptional functional group tolerance, avoidance of stoichiometric oxidized phosphine by-products, and generation of the halogenated compounds in high yields under mild reaction conditions. Moreover, the cost-effective nature of $Ru(bpy)_3Cl_2$, low catalyst loadings, operational simplicity and activity under visible-light irradiation makes this transformation industrially valuable.

Methods

A flame-dried 10 ml Schlenk flask with a rubber septum and magnetic stir bar was charged with tris(2,2′-bipyridyl)ruthenium(II) chloride hexahydrate (5.0 μmol, 0.010 equiv.), the corresponding alcohol (0.50 mmol, 1.0 equiv.), carbon tetrabromide (1.0 mmol, 2.0 equiv.) and sodium bromide (1.0 mmol, 2.0 equiv.). The flask was purged with a stream of nitrogen, and dry DMF (5.0 ml) was added with a syringe. The mixture was degassed by the freeze–pump–thaw procedure (three cycles), and placed in a 250 ml beaker with blue LEDs wrapped inside (the reaction reaches temperatures between 25 and 30 °C upon exposure to the blue LEDs). The reaction mixture was stirred until it was complete (as judged by thin layer chromatography analysis). The mixture was poured into a separatory funnel containing 25 ml Et_2O and 25 ml H_2O. The layers were separated and the aqueous layer was extracted with Et_2O (2 × 25 ml). The combined organic layers were washed with saturated $Na_2S_2O_3$ solution, brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography on silica gel to afford the desired product.

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Author contributions

C.D. performed the experiments. All authors conceived and designed the experiments, analysed the data, contributed to discussions and wrote the manuscript.

Additional information

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