

Bromine as a Visible-Light-Mediated Polarity-Reversal Catalyst for the Functionalization of Aldehydes

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Abstract

Polarity-reversal catalysts enable otherwise sluggish or completely ineffective reactions which are characterized by unfavorable polar effects between radicals and substrates. We herein disclose for the first time that when irradiated by visible light, bromine can behave as a polarity-reversal catalyst. Hydroacylation of vinyl arenes, a three-component cascade transformation and deuteration of aldehydes were each achieved in a metal-free manner without initiators by using *N*-bromosuccinimide as the precatalyst. Light is essential to generate and maintain the active bromine radical during the reaction process. Another key to success is that HBr can behave as an effective hydrogen-donor to turn over the catalytic cycles.

Introduction

The “polar effect” is one of the paramount factors that determine the reactivity of radicals. It has been widely exploited in radical chemistry to obtain desired reactivity and selectivity.¹⁻³ This is especially important in the domain of radical-based C-H functionalization, which can differentiate the various C-H bonds in organic molecules.⁴⁻⁸ In this context, the emergence of photocatalysis has provided enormous opportunities for C-H functionalization through direct photo hydrogen atom transfer (HAT) catalysis or by the synergistic combinations of photoredox with HAT catalysis.⁹⁻¹⁸ Aldehydes, one of the most abundant and readily available feedstocks, are enabled to generate acyl radicals to achieve umpolung reactivity by photo-induced HAT in a step- and atom-economic fashion.¹⁹⁻²⁰ However, the acceptors of acyl radicals were limited to electron-deficient alkenes and radical trappers containing electron-withdrawing leaving groups,²¹⁻²⁵ to result in an electrophilic radical intermediate to turn over the redox-neutral photocatalytic cycle (Fig. 1a). On the other hand, polarity reversal catalysis (PRC), established decades ago, has found broad applications in radical hydrogen atom transfer (HAT) processes.²⁶⁻²⁸ Otherwise sluggish or completely ineffective reactions could, therefore, be accomplished by replacing a polarity-mismatched step with a two-step process in which the radicals and substrates are polarity-matched. In contrast to redox-neutral photocatalysis, the resulting radical adduct from the reaction between the acyl radical and radical trappers needs to be nucleophilic to finish the PRC catalytic cycle. Thiols and *N*-hydroxyphthalimide (NHPI) have been employed as PRCs for hydroacylation with electron-rich alkenes.²⁹⁻³² However, catalytic or stoichiometric radical initiators are required to generate the active thiyl and oxy radicals to induce the PRC. The discovery of new polarity-reversal catalysts that can avoid the use of radical initiators will enable greener radical transformations.

Bromine and sulfur are diagonal relationships in the periodic table which possess many similar characters. Thiol is the most common PRC catalyst with notorious toxic and odiferous characters (Fig. 1b). In stark contrast, bromine reagents have not been utilized in PRC reactions, but bromine radical (Br·) is well known as a moderately electrophilic HAT agent, which can abstract hydrogen atoms from C-H bonds to form nucleophilic carbon radicals.^{11,33-37} In this context, Ryu et al. have developed various attractive bromine-radical mediated transformations.³⁵⁻³⁷ Very recently, the Miyake group described an

excellent study of bromine radical catalysis promoted by energy transferring photosensitization.³⁸ Our group has reported photo-induced selective tertiary C(sp³)-H alkylation and amination using CH₂Br₂ as a bromine radical precursor.¹¹ Published work has indicated that both Br₂ (with a bond dissociation energy, BDE = 194 kJ/mol) and NBS (*N*-bromosuccinimide, BDE = 243 kJ/mol) undergo reversible homolytic cleavage by visible-light photolysis (470 nm blue photon energy = 254 kJ/mol) to reversibly generate active bromine radicals.³⁹⁻⁴⁰

We envisioned that by taking advantage of visible-light promoted homolysis of bromine reagents, bromine radical formed may behave as an effective polarity-reversal catalyst without the requirement of an external radical initiator, and result in a complementary substrate scope to photoredox catalysis. Herein, we report that bromine acts as an efficient polarity-reversal catalyst for radical transformations with aldehydes (Fig. 1c). This strategy features a broad scope of applications, including hydroacylation of vinyl arenes, a three-component cascade transformation, and deuteration of aldehydes. The bromine radical will promote a HAT from an aldehyde substrate to deliver hydrogen bromide and an acyl radical which will subsequently react with a radical trapper to give another transient nucleophilic radical adduct. Finally, the polarity-matched HAT between the nucleophilic radical adduct and HBr will furnish the final product, with the regeneration of the active bromine radical which can participate in another polarity reversal catalytic cycle.

Results

Reaction optimization. The feasibility of this concept was first investigated in a bromine-catalyzed hydroacylation of styrene with two equivalents of hexanal. After an extensive evaluation (Supplementary Table S1), we established that a combination of NBS (15 mol%) in PhF (0.025 M) at 80 °C under blue LED irradiation was optimal and produced the desired ketone product **3a** in 66% isolated yield. No decarbonylated product was detected at this elevated temperature (80 °C). Other bromine sources such as Br₂,⁴⁰ CBr₄,⁴¹ and BnBr⁴² also generated the desired product, albeit with lower efficiency. However, (*n*-Bu)₄N-Br failed to promote this transformation. The solvent has a large impact on the reaction outcome and the formation of the product was observed only in aromatic organic solvents (e.g., PhCl, 33% yield; benzene, 46% yield). Use of other non-aromatic solvents such as MeCN, DMF, and EtOAc gave no product. A lower reaction temperature (50 °C) resulted in a significantly decreased yield of 16%. The yield of product can be improved to 71% by adding NBS in two portions sequentially (10 mol% NBS followed by additional 5 mol% NBS after 36 hours). Control experiments showed that light was essential for this transformation. Replacing NBS with PhSSPh could not lead to the formation of product under the optimized conditions (Supplementary Table S1).

Substrate scope. With the optimal conditions in hand, we investigated the substrate scope of the hydroacylation of vinyl arenes **2**. As demonstrated in Fig. 2a, a broad scope of aliphatic aldehydes was effective and provided the ketone products in moderate to good yields. Primary aldehydes which are readily available feedstocks, participated smoothly in hydroacylation reactions (**3a-3f**). Some sensitive

functionalities such as a terminal ester (**3e**) and alkyne (**3f**) were tolerated in this radical transformation. Secondary aldehydes, either acyclic (**3g**), cyclic (**3h**), or heterocyclic (**3i**), were all viable coupling partners. Compared to aliphatic aldehydes, aromatic aldehydes were less reactive, producing the corresponding products (**3j-3l**) in moderate yields (42-56%). The generality of this hydroacylation with respect to the vinyl arene component was subsequently investigated. A wide range of functionalities, including aryl bromides (**3m, 3n**), acetate (**3o**), cyanide (**3q**), tosylate (**3r**), and acid (**3s**) were tolerated. 2-Vinylnaphthalene was also a suitable substrate for the hydroacylation, delivering product **3t** in good yield (75%). In addition, phosphine oxides could also be converted to corresponding organophosphorus compounds (**3u, 3v**). When pivaldehyde and diphenylacetaldehyde were applied to this protocol, decarbonylation was detected, and no desired product could be obtained (Supplementary Fig. S1 and S2). Moreover, no reaction occurred when acrylates **4** were used in place of vinyl arenes **2**, owing to the mismatched polarity between the radical adduct and HBr.

Multi-component radical cascade reactions play a privileged role in organic synthesis and enable direct construction of complex and diverse molecular scaffolds.^{7, 43-44} The failure of hydroacylation with acrylates **4** and the radical nature of this PRC led us to search for a possible bromine-catalyzed three-component coupling reaction. We speculated that the bromine-induced nucleophilic acyl radicals from aldehydes would preferentially add to electron-deficient acrylates in the presence of vinyl arenes. The generated α -acyl radical was relatively electrophilic and would be expected to couple with vinyl arenes instead of undergoing an unfavorable HAT with HBr. The intended three-component PRC reactions were realized effectively with coupling aldehydes **1**, unsaturated esters **4** and vinyl arenes **2**, generating densely functionalized 1,4-dicarbonyl compounds in a highly selective manner (Fig. 2b). Such useful products would be difficult to access otherwise, and related reports usually require excess oxidants for quenching the nucleophilic radical adduct.⁴⁵⁻⁴⁶ Primary (**5a-5c**), secondary (**5d-5f**), and aromatic (**5g-5j**) aldehydes were all effective substrates for this cascade transformation, leading to 1,4-dicarbonyl products in moderate to good yields (41-79%). To further demonstrate the diversity of this transformation, acrylates **4** containing various functionalities, such as benzyl, trifluoromethyl, ether, chloride, and isobornyl groups participated smoothly to afford the corresponding products (**5k-5p**) in good yields (64-75%). Various vinyl arenes were applied in this protocol which illustrated good tolerance of functionalities (**5q-5v**). Functional groups such as the aryl chloride (**5q**) and bromide (**5u**) provided handles for further diversification.

In addition, we hypothesized that the bromine-induced nucleophilic acyl radicals may trap a deuterium atom from D-Br in a polarity-matched manner, thus realizing deuteration of aldehydes. The D-Br could be formed by rapid H/D exchange between HBr and D₂O. The intended deuteration of aromatic aldehydes proceeded well in the presence of 25 equivalents of D₂O using solely NBS as the catalyst under blue LED irradiation. All electron-deficient and electron-rich aromatic aldehydes delivered products in generally good to excellent isolated yields and deuterium incorporation (Fig. 2c). Functionalities ranging from electron-withdrawing substituents such as halides, trifluoromethyl groups, and boronate esters (**6a-6e**), to electron-donating substituents, such as phenyl (**6f**), alkyloxy (**6g-6j, 6n**), diphenylamino (**6k**), tert-butyl (**6l**),

and methylthio (**6m**) groups, were tolerated well. However, aliphatic aldehydes were less effective in the H/D exchange process, and only low deuterium incorporations in the aldehyde C-H bond (**6r-6t**) were achieved. This may be due to the keto-enol tautomerization of aliphatic aldehydes in the presence of excess D₂O,⁴⁷ which was suggested by the deuteration of the α -positions of the formal groups. The successful H/D exchange also confirmed the formation of acyl radicals under light-promoted conditions. Notably, no deuteration was detected at the benzylic positions.

Further synthetic applications. Encouraged by the broad substrate scope of the bromine-based PRC protocols, the potential of this strategy for the late-stage site-selective functionalization of complex molecules was subsequently investigated (Fig. 3a). Aldehydes derived from natural products such as (+)-fenchol and lithocholic acid, participated in hydroacylation smoothly to afford products **7** and **8** in moderate yields. H/D exchange of derivatives from *L*-menthol, epiandrosterone, and cholesterol resulted in high deuterium incorporation with excellent chemoselectivity of the aldehydic C-H bonds. No tertiary-carbon functionalization could be detected in above transformations, even though Br radical has been reported as a suitable HAT agent for tertiary C-H bonds.^{11,37} The synthetic value of this method was further demonstrated by the diversification of the synthesized products (Fig. 3b). D-labeled alkenes can be easily obtained from deuterated benzaldehydes by Horner-Wadsworth-Emmons olefination.⁴⁸ Treatment of 1,4-diketones that generated from the radical cascade reaction with NaBH₄ followed by TsOH produced lactones **12** in good yields albeit in low diastereoselectivity.⁴⁹

Mechanistic elucidation with supporting evidence. A series of control experiments were performed to reveal more hints concerning the mechanisms of the aforementioned transformations (Fig. 4a). A deuterium-labeling experiment was conducted by adding D₂O to the hydroacylation reaction. This resulted in a 55% yield of deuterium-containing 1-phenyl-3-octanone **3a'**, where deuteration took place at the α -positions of the carbonyl group and benzylic positions. When **3a** was treated with D₂O under the same conditions, deuteration was only detected at the α -positions of the carbonyl group (**3a''**). These results indicate that keto-enol tautomerism⁴⁷ promoted the deuteration at the α -positions of the carbonyl group, and this is consistent with the results of deuterated aldehydes **6r-6t** (Fig. 2c). The 26% deuteration of **3a'** at the benzylic positions suggested a HAT between a generated benzylic radical and H/D-Br. No product could be detected under the standard hydroacylation conditions in the presence of TEMPO, supporting a radical pathway. The light on/off experiment indicated that photolysis is essential for the reformation of Br radicals to sustain the radical chain process. UV-Vis measurements indicate that both NBS and Br₂ absorb and can be activated by light in the range of 400 to 600 nm (Supplementary Fig. S7 and S8).

In light of all experimental data and previous literature reports,^{35-38,50} plausible mechanistic pathways for photo-mediated bromine-catalyzed PRC reactions are proposed and illustrated in Fig. 4b. Even though the homolysis of NBS to bromine radicals could be induced by blue light irradiation,³⁷ this process might be accelerated by heating under our optimal conditions. The generated bromine radicals can recombine to form Br₂, which explains the requirement of constant light irradiation for the homolysis of Br₂ back to the

desired Br radicals. The Br radical abstracts a hydrogen atom from aldehyde **1** to produce an acyl radical **I**. When vinyl arenes **2** were utilized to trap the acyl radical, the resulting benzylic radical **II** can subsequently undergo a polarity-favored HAT with HBr to produce ketone product **3**. Alternatively, in the presence of acrylate **4**, the nucleophilic acyl radical **I** will preferentially add to electron-deficient acrylates rather than to vinyl arenes. In this way, an electrophilic radical adduct **III** is formed, which is polarity-mismatched with H-Br and will couple instead with vinyl arene **2**. The resulting benzylic radical **IV** finally can trap a hydrogen atom from HBr to give the 1,4-dicarbonyl product **5**. In the deuteration reaction, the acyl radical **I** will abstract the deuterium atom from D-Br, which is generated from the rapid H/D exchange between D₂O and HBr.

Density functional theory (DFT) calculations were conducted to further support the proposed mechanism of hydroacylation. The calculated potential energy surface (PES) was illustrated in Fig. 5a. The reaction started with a process of bromine radical abstracting the hydrogen atom from propionaldehyde to deliver **INT1**, which was an easy process without transition state (Fig. 5b). The subsequent radical addition to styrene led to a radical adduct **INT2** with an energy barrier of 11.6 kcal/mol. The HAT between hydrogen bromide and **INT2** gave an energy barrier of 7.0 kcal/mol to deliver the product. The pathway of **INT2** abstracting the hydrogen atom from propionaldehyde was unlikely due to a higher energy barrier of 23.6 kcal/mol.

In summary, we have disclosed for the first time, to the best of our knowledge, that bromine can be utilized as a polarity-reversal catalyst under visible-light irradiation. Hydroacylation of vinyl arenes, a three-component 1,2-difunctionalization of acrylates, and a deuteration of aldehydes were achieved in an atom- and step-economic and highly selective manner. The key to the success relies on the constant light-irradiation which induces and maintains bromine radicals for an active chain process. Compared to conventional PRC, this photo-mediated bromine-based PRC is distinguished by its green characters which stem from its no requirement of any chemical initiators.

Methods

General procedure for hydroacylation of vinyl arenes. In the glovebox, aldehyde **1** (0.4 mmol, 2 equiv) and alkene **2** (0.2 mmol, 1 equiv), PhF (8 mL), and NBS (0.02 mmol, 0.1 equiv) were added to a sealed tube equipped with a magnetic stirring bar. Then, the reaction mixture was irradiated by blue LED lamps (2 x 40 W) and magnetically stirred at 80 °C. After 36 hours, NBS (0.01 mmol, 0.05 equiv) was added and the reaction mixture was stirred and irradiated for an additional period of 36 hours. The reaction was quenched with water (5 mL), extracted with EtOAc (3 x 5mL) and the combined organic layers were dried over Na₂SO₄ and concentrated. The product was purified by column chromatography (SiO₂).

General procedure for three-component cascade transformation. In the glovebox, aldehyde **1** (0.4 mmol, 2 equiv) and alkene **2** (0.2 mmol, 1 equiv), acrylate **4** (0.6 mmol, 3 equiv), PhF (8 mL), and NBS (0.02 mmol, 0.1 equiv) were added to a sealed tube equipped with a magnetic stirring bar. Then, the reaction mixture was irradiated by blue LED lamps (2 x 40 W) and magnetically stirred at 80°C. After 36 hours, NBS (0.01

mmol, 0.05 equiv) was added and the reaction mixture was stirred and irradiated for an additional period of 36 hours. The reaction was quenched with water (5 mL), extracted with EtOAc (3 x 5 mL) and the combined organic layers were dried over Na₂SO₄ and concentrated. The product was purified by column chromatography (SiO₂).

General procedure for deuteration of aldehydes. In the glovebox, aldehyde **1** (0.2 mmol, 1 equiv), D₂O (5 mmol, 25 equiv), PhF (4 mL), and NBS (0.02mmol, 0.1 equiv) were added to a sealed tube equipped with a magnetic stirring bar. Then, the reaction mixture was irradiated by blue LED lamps (2 x 40 W) and magnetically stirred at 80 °C. After 72 hours, the reaction solution was concentrated, and the product was purified by column chromatography (SiO₂).

Computational details. All density functional theory (DFT) calculations were conducted with the Gaussian 09 program,⁵¹ using the popular functionals of (U)B3LYP-D3(BJ).⁵²⁻⁵⁵ Geometry optimizations were carried out with the basis set of 6-31+G(d, p) basis set for all atoms. Structures were optimized with Truhlar's SMD method (Solvation Model based on the Quantum Mechanical Charge Density) and Benzene was chosen as the solvent. Vibrational frequency analysis confirmed that the structure was either a minimum or a transition state. The calculation of single-point energy using SMD model (Benzene) and (U)B3LYP-D3(BJ) method (with the 6-311++G(3df, 3pd) basis set for all atoms). All relative enthalpy and Gibbs free energies (at 298.15K and 1 atm) are reported in kcal mol⁻¹.

Declarations

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Author contributions

H.W. and H.L. discovered and developed the reaction. H.W. and J.W. conceived and designed the investigations. M.H. and X.S. conducted density functional theory (DFT) calculations. H.W., H.L., T.W., X.C., J.Y., and M.W. performed the experiments. H.W. and J.W. wrote the manuscript.

Additional information

Supplementary Information accompanies this paper at <http://www.nature.com/naturecommunications>

Competing financial interests: The authors declare no competing financial interests.

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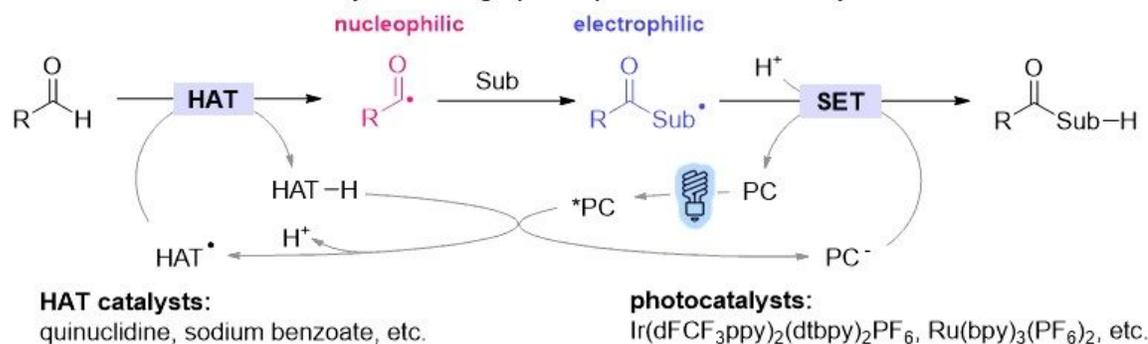
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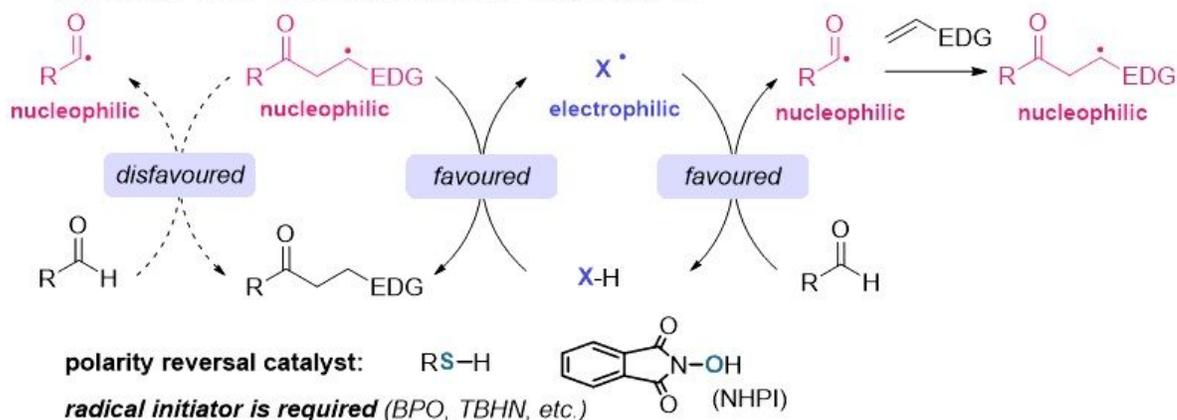
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Figures

a. Functionalization of aldehydes through photo-promoted HAT catalysis



b. Functionalization of aldehydes through traditional PRC



c. Development of bromine radicals as polarity-reversal catalysts (this work)

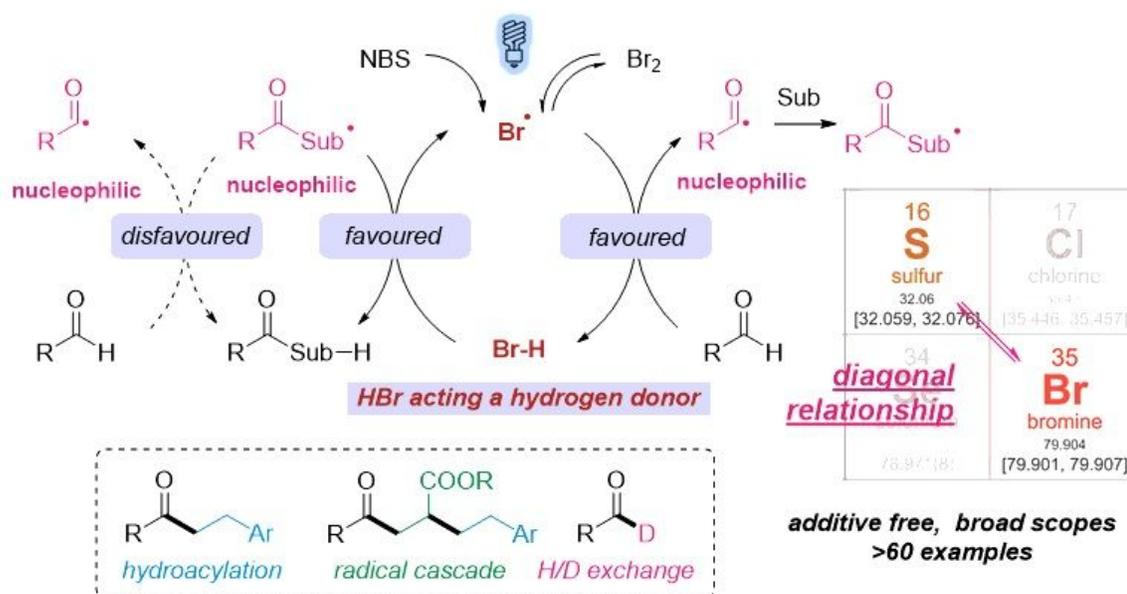


Figure 1

Development of bromine radicals as visible-light-mediated polarity-reversal catalysts. a Functionalization of aldehydes through photo-promoted HAT catalysis. b Functionalization of aldehydes through traditional PRC. c Development of bromine radicals as polarity-reversal catalysts (this work).

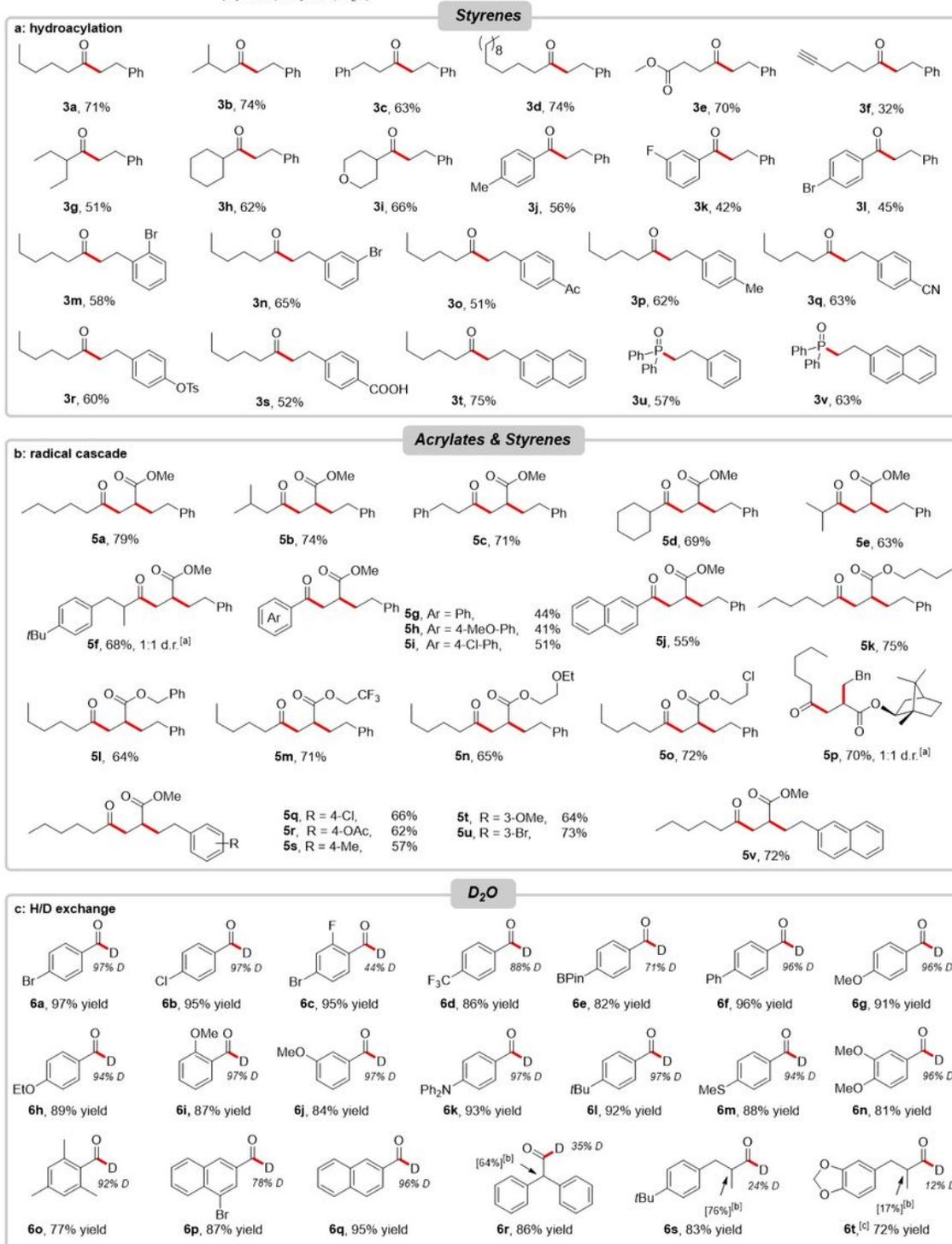
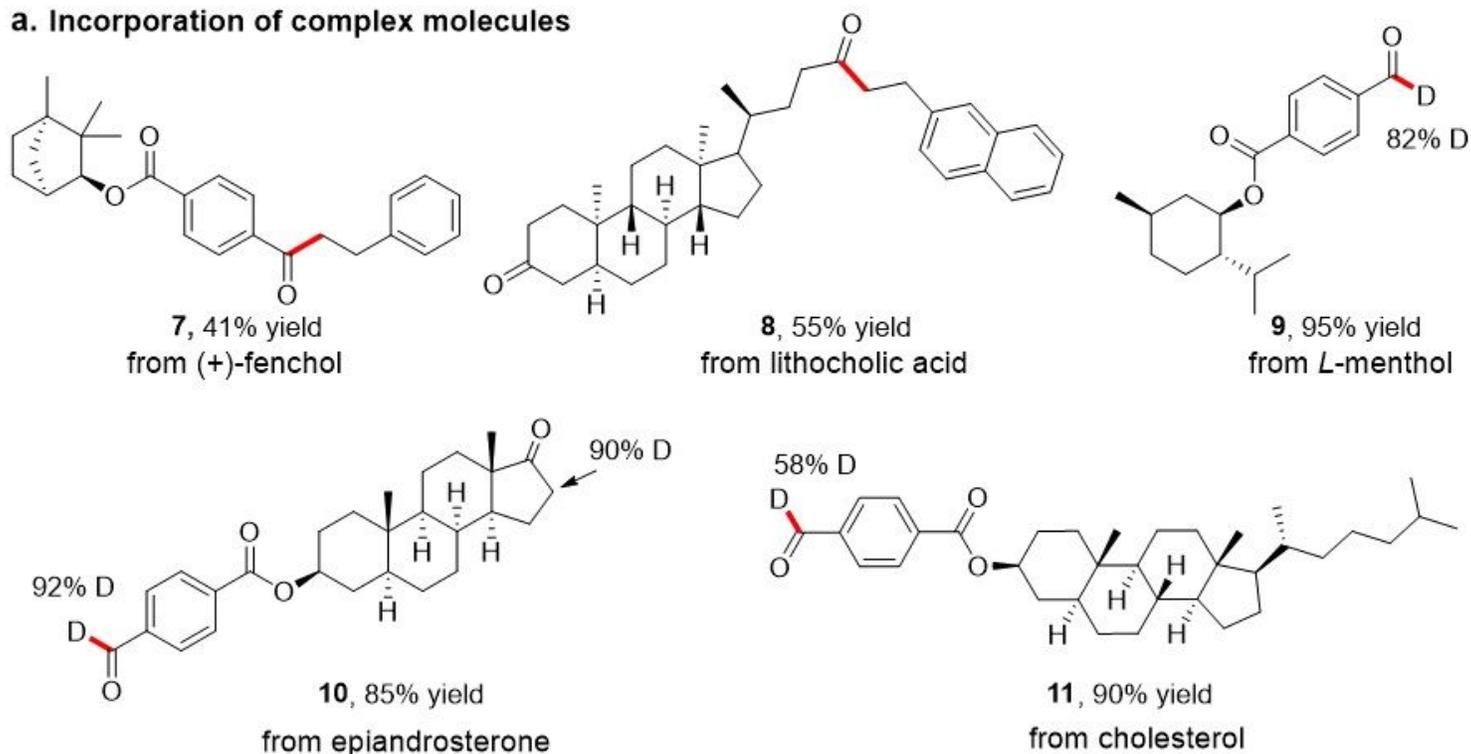


Figure 2

Scope of bromine catalyzed functionalization of aldehydes. Isolated yields. Performed with alkene (0.2 mmol) and aldehydes (0.4 mmol) in hydroacylation. Performed with alkene (0.2 mmol), acrylate (0.6 mmol), and aldehydes (0.4 mmol) in cascade reaction. Performed with alkene (0.2 mmol) and D₂O (5 mmol) in deuteration. See Supplementary Information for experimental details. aDr values were determined by analysis of ¹H NMR spectra of the crude product mixture. b δ -Carbonyl C-H bonds in

compounds 6r-6t were deuterated, with the deuteration incorporation shown in square brackets. cReaction time of 36 h.

a. Incorporation of complex molecules



b. Synthetic utility of products

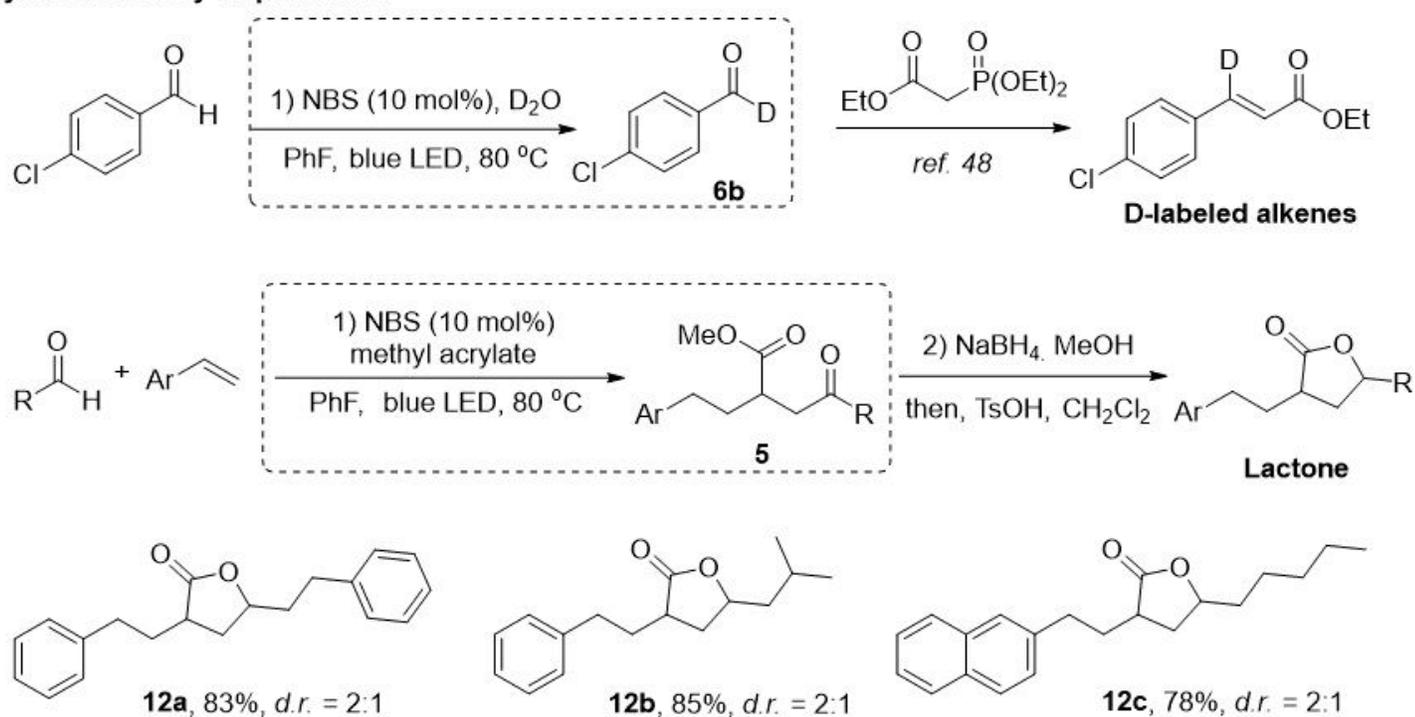


Figure 3

Synthetic application. a Incorporation of complex molecules. b Further synthetic application. Dr values were determined by analysis of ¹H NMR spectra of the crude product mixture.

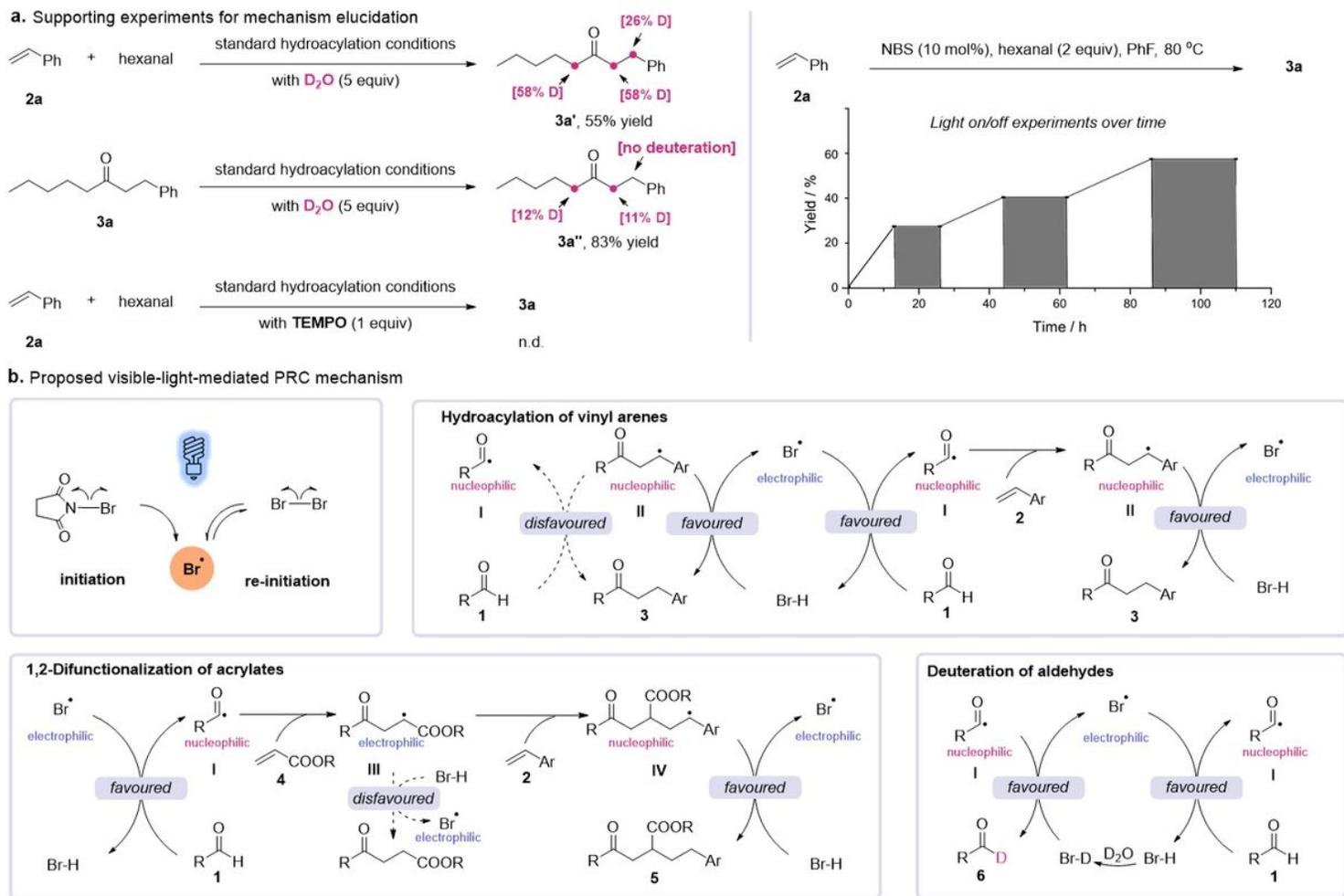


Figure 4

Proposed mechanism and supporting evidence. a Supporting experiments for mechanism elucidation. b Proposed visible-light-mediated PRC mechanism.

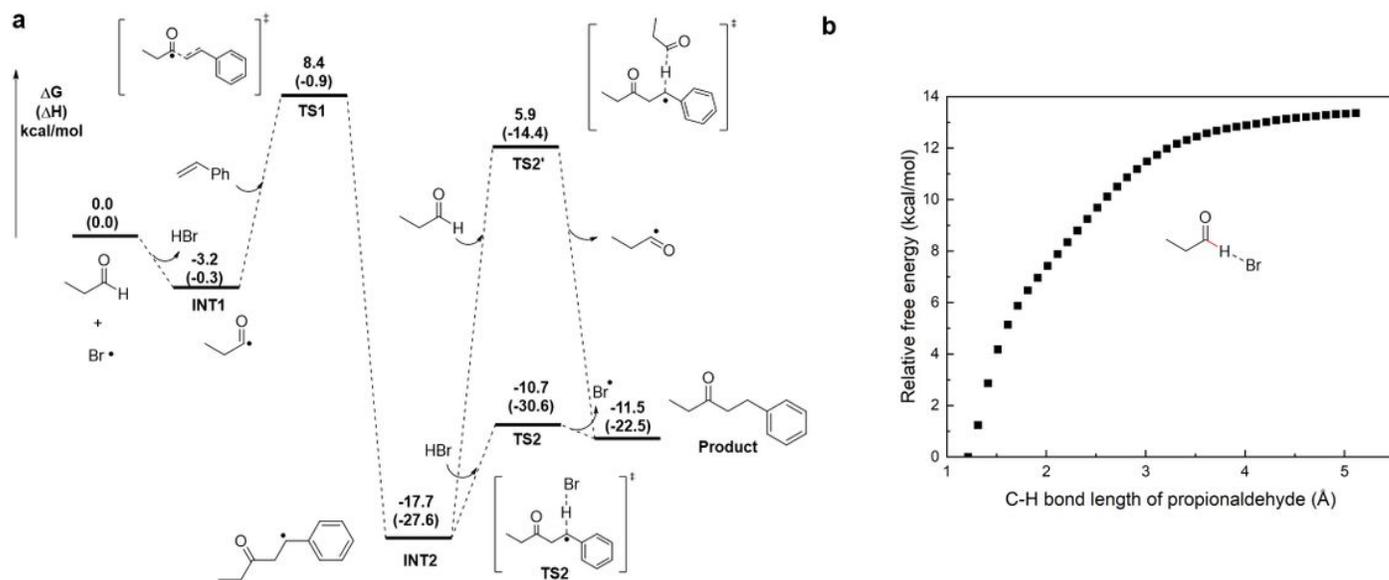


Figure 5

DFT calculations. a PES of hydroacylation. b Results of scanning the C-H bond of propionaldehyde in bromine radical HAT process. Relative free energies are in kcal/mol.

Supplementary Files

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