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ARTICLE

Photo-induced dehalogenative deuteration and elimination of alkyl halides enabled by phosphine-mediated halogen-atom transfer

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Dehalogenative deuteration of organic halides is an efficient and straightforward method for incorporating deuterium atoms at specific locations within target molecules. However, utilizing organic halides in photoredox chemistry, particularly with unactivated alkyl halides, presents challenges due to their low reduction potentials. In this work, we present a general and effective photoinduced dehalogenative deuteration method for a diverse array of alkyl halides, employing D_2O as an economical source of deuterium. The use of Cy_3P as a halogen-atom transfer reagent facilitates the dehalogenation of alkyl halides. This method demonstrates a broad scope, with over 70 examples, and shows excellent tolerance for various alkyl halides. The precise dehalogenation of complex alkyl halides highlights the potential of this protocol for late-stage dehalogenative deuteration of natural product derivatives and pharmaceutical compounds. Additionally, the dehalogenative elimination of unactivated alkyl halides can be also achieved by integrating photoredox and cobalt catalysis using the same halogen-atom transfer agents.

Introduction

Deuterium-labeled compounds play a significant role in organic synthesis and pharmaceutical chemistry.[1] In particular, incorporating deuterium atoms into bioactive compounds can enhance the absorption, distribution, metabolism, and excretion properties of drug candidates while preserving their biological potency.[2] For example, deutetrabenazine and deucravacitinib have been approved by FDA in succession over the past few years, and numerous deuterated drug candidates have entered clinical trials (Scheme 1a).[3] Thus, their importance as medicinally privileged functionalities has driven the development of effective deuteration methods to access these deuterium-containing molecules. Among the current methods for synthesizing deuterium-containing compounds, direct hydrogen isotope (H/D) exchange is generally considered one of the most efficient and straightforward strategies.[4] However, this methodology still faces significant limitations, such as low deuterium incorporation and unsatisfactory regioselectivity. Dehalogenative deuteration from organic halides represents a key alternative method for obtaining deuterated target compounds, as it allows for the incorporation of deuterium atoms at specific positions. Consequently, a range of environmentally friendly photocatalytic and organic electrochemical strategies have been explored for C-X/C-D exchange.[5]

Organic halides are important and versatile compounds, but their use in photoredox chemistry is limited by their highly negative reduction potentials (E_{red} < -2.0 V vs SCE for unactivated alkyl iodides).[6] In recent years, the development of halogen-atom transfer (XAT) processes has made significant strides in generating carbon radicals for synthetic chemistry.[7] Within this framework, several innovative methods for cleaving carbon-halogen bonds have been focused on advancing dehalogenative deuteration through XAT pathways. For example, the Renaud group developed an excellent deuterative deiodination of alkyl iodides using Et_3B as the XAT reagent (Scheme 1b, *i*).[8] Leonori and Juliás demonstrated that strongly nucleophilic α-aminoalkyl radicals could be designed as XAT reagents for dehalogenative deuteration reaction, thus expanding the scope beyond the previously limited alkyl iodides albeit with lower conversion rates (Scheme 1b, *ii*).[9] More recently, Lee et al. reported a thiyl radical-catalyzed deuterative debromination reaction of alkyl and aryl bromides using a stoichiometric amount of $(TMS)_3SiH$ as the XAT reagent (Scheme 1b, *iii*).[10] Despite the advantages demonstrated by these XAT-mediated transformations, the development of general and robust strategies for the dehalogenative deuteration of organic bromides or chlorides with novel XAT reagents remains an attractive and highly desirable goal.

Recent advances in phosphine-mediated radical chemistry have shown that using phosphoranyl radicals via homolytic cleavage provides an efficient and straightforward route to access diverse radical species for further transformations.[11] With the advent of visible light catalysis, phosphoranyl radicals can be generated under

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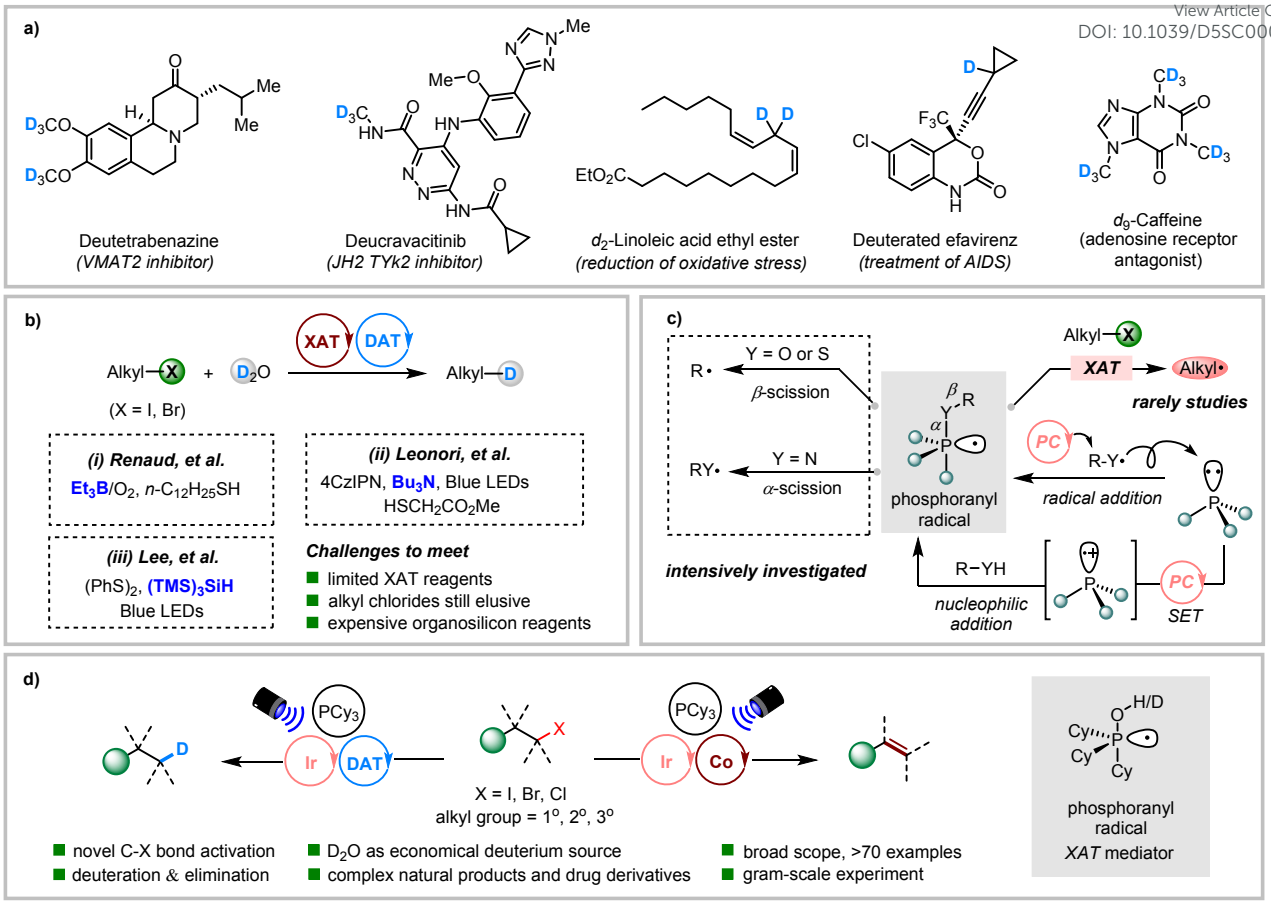

Scheme 1 Current status for dehalogenative deuteration via halogen atom transfer and our reaction design.

mild conditions through radical addition or single-electron oxidation followed by nucleophilic addition (Scheme 1c). In this context, the application of phosphoranyl radicals for deoxygenation and desulfurization reactions via *β*-scission has been extensively investigated.[12] More recently, Doyle et al. achieved the homolytic cleavage of the P–N bond via *α*-scission to facilitate the hydroamination of olefins with primary sulfonamides or azoles.[13] However, the synthetic application of phosphoranyl radicals through the XAT pathway with alkyl halides remains an intriguing frontier in contemporary research and is yet to be fully explored.[14] The highly nucleophilic nature of phosphoranyl radicals[15] may lead to kinetic polar effects that enhance the XAT process.

Herein, we report an unprecedented photocatalytic deuterodehalogenation of unactivated alkyl halides using photoredox and thiol organocatalysis, with PCy_3 serving as the halogen-abstracting reagent (Scheme 1d). Furthermore, the dehalogenative elimination of unactivated alkyl halides can also be achieved by integrating photoredox with cobalt catalysis using the same halogen-atom transfer agents. Notable features of this protocol include (1) novel C-X bond activation, (2) broad functional group tolerance (> 70 examples), (3) D_2O as an economical deuterium source, and (4) late-stage deuteration of complex natural products and drug derivatives.

Results and discussion

Our study began with the optimization of photocatalytic deuterondehalogenation of 4-bromo-1-tosylpiperidine (**1a**) with D_2O. The optimized reaction conditions were successfully achieved by using **PC1** (1 mol%) as a photocatalyst, 2,4,6-triisopropylbenzenethiol (HAT1, 10 mol%) as the co-catalyst for deuterium atom transfer,[16] **P1** (2.5 equiv.) as a halogen-atom transfer reagent, and CH_3CN/D_2O (5:1/ *v*/*v*) as the solvent under 455 nm light irradiation. Gratifyingly, the deuterated product **2a** was obtained in 91% yield with 95% deuterium incorporation (D-inc.) using commercially inexpensive D_2O as an ideal deuterium source (Table 1, entry 1). The use of tris(4-methoxyphenyl)phosphane (**P2**) and triphenylphosphine (**P3**) led to unsatisfying results (entries 2 and 3). In addition, the deuterondehalogenation could not occur in the absence of phosphine mediator (entry 4), suggesting that the halogen-transfer reagent was crucial for the success of the reaction. Other thiol co-catalysts were employed under the same conditions, and the reaction yield decreased to varying degrees, although D inc. remained at a high level (entries 6-7). Upon evaluating a selection of frequently used photocatalysts (See SI, Table S2), we found that photocatalysts with excited state oxidation potentials below that of PCy_3 were ineffective to the reaction. Ir-based photocatalysts (**PC2**) were explored but

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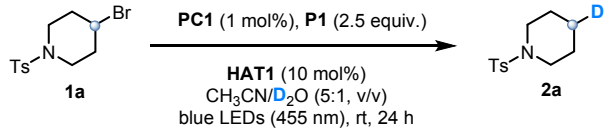
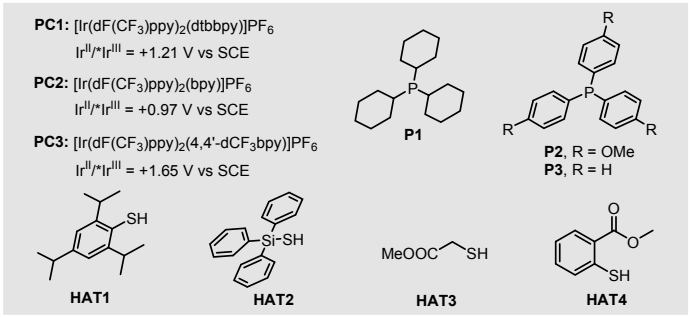
provided no improvement over **PC1** (entries 8). Furthermore, catalysts with higher oxidation potentials also led to decreased yields likely due to over oxidation of the phosphoranyl radical (PC3). Moreover, optimization studies were carried out by screening a variety of solvents, such as DMSO, THF, and DMF, but they all provided unsatisfactory results (entries 10-12). Control experiments demonstrated that light irradiation and photocatalyst are both requisite for the desired transformation (entries 13 and 14), while the use of TRIP thiol significantly increased the yield (entry 15).

Table 1. Optimization studies [a]



entry	Variation of standard conditions	yield (%)[b]	D-inc. (%)[c]
1	None	91	95
2	**P2** instead of **P1**	25	90
3	**P3** instead of **P1**	<5	-
4	no **P1**	N.D.	-
5	**HAT2** instead of **HAT1**	62	94
6	**HAT3** instead of **HAT1**	81	91
7	**HAT4** instead of **HAT1**	88	87
8	**PC2** instead of **PC1**	79	93
9	**PC3** instead of **PC1**	12	-
10	DMSO as solvent	41	83
11	THF	26	76
12	DMF	19	85
13	no light	N.D.	-
14	no photocatalyst	N.D.	-
15	no **HAT1**	35	95



[a] Reaction conditions: **1a** (0.20 mmol, 1.0 equiv.), **PC1** (0.002 mmol, 1 mol%), **P1** (0.50 mmol, 2.5 equiv.), **HAT1** (0.02 mmol, 10 mol%) in CH_3CN/D_2O (2.0 mL, v/v = 5:1, 0.1 M) at room temperature under Ar atmosphere, 455 nm LEDs (10 W), 24 h. [b] Yields are of isolated products after chromatographic purification. [c] D-inc. determined by ^1H NMR. Ts = *p*-toluenesulfonyl. PC = photocatalyst. HAT = Hydrogen atom transfer. D-inc. = Deuterium incorporation. N.D. = Not detected.

Dehalogenative deuteration of alkyl halides

Under the existing optimized conditions, we investigated the scope of the deuterondehalogenation with respect to the alkyl halides, as shown in Scheme 2. It is noteworthy mentioning that the developed phosphoranyl radical assisted dehalogenation could overcome the limitation of the highly negative reduction potentials of alkyl halides, and thus a wide variety of unactivated secondary alkyl bromides was first investigated. In most case, good yields, and high levels of D-incorporation of the products (73-91 yields, 89-97% D-inc.) were formed. Cyclic bromides were found to be suitable C(sp^3)-X substrates, which were smoothly converted into the desired deuterated (**2a**-**2c**) in 73-91% yields. Bromoalkanes containing two aromatic rings could also be applied to give (**2d**) in 87% yield (96% D-inc.). Different lengths of carbon chains were all well tolerated in our XAT strategy, and gave the products (**2e**-**2g**) in 79-91% yields. Several activated secondary alkyl bromides were also tested, providing the deuterated products (**2h**-**2j**) in good efficiency with moderate to high D-incorporation.

Next, we turned our attention to more challenging unactivated primary alkyl bromides. A wide range of primary alkyl bromides bearing amide or ester moieties were amenable to our strategy, delivering the corresponding deuterated products (**2k–2o**) in 63–81% yields with high deuterium incorporation (> 90%). Besides, heterocyclic aromatics including pyridine and thiophene were also found to be competent substrates, giving the desired products **2p** and **2q** in 85% and 61% yields with high D-incorporation, respectively. Furthermore, other alkyl bromides, especially tertiary substrates that did not work well in previous studies,[17] were found to be well compatible using our method and yielded the desired products (**2r**-**2v**) in satisfactory D-incorporation. Moreover, the use of activated primary alkyl bromides as substrates gave the corresponding deuterated products **2w** and **2x** in 82% and 72% yields, respectively. Dibromomethylene unit was then subjected to test the adaptability of our XAT method, furnishing the desired monodeuterated products **2y** and **2z** in good yields with excellent D-incorporation (both 99% D). Interestingly, alkyl chlorides at benzylic and tertiary alkyl positions also proved to be viable substrates (**2aa** and **2ab**).

To further demonstrate the practical of the method, late-stage deuteration of complex molecules were conducted using our XAT strategy. The deuterodehalogenation of pharmaceuticals derivatives including estrone (**2ac**), triclosan (**2ad**), DL-menthol (**2ae**), and probenecid (**2aj**) was successfully achieved in 62-79% yield with 94-97% D-incorporation. The nonsteroidal analgesics or anti-inflammatory, such as ibuprofen (**2af**), naproxen (**2ag**), zaltoprofen (**2ah**), and nabumetone (**2ai**) can also be reacted smoothly in this protocol. In addition, amino acid (**2ak**) and glucose derivatives (**2al**) that widely exist in organisms were also effectively transformed into deuterated products in 75% and 65% yields. Furthermore, the generality and practicality of this strategy to tertiary bromides can be further extended to complex pharmaceuticals (**2am** and **2an**). The incorporation of a deuterium atom to a parent drugs and drug candidates can dramatically enhance the metabolism and pharmacokinetic properties, without altering their desired traits.[18] Clofibrate is a lipid-lowering drug that is also effective in the treatment of neonatal jaundice.[19] Utilizing our strategy, deuterated clofibrate (**2ao**) was smoothly achieved from commercially available clofibric acid.

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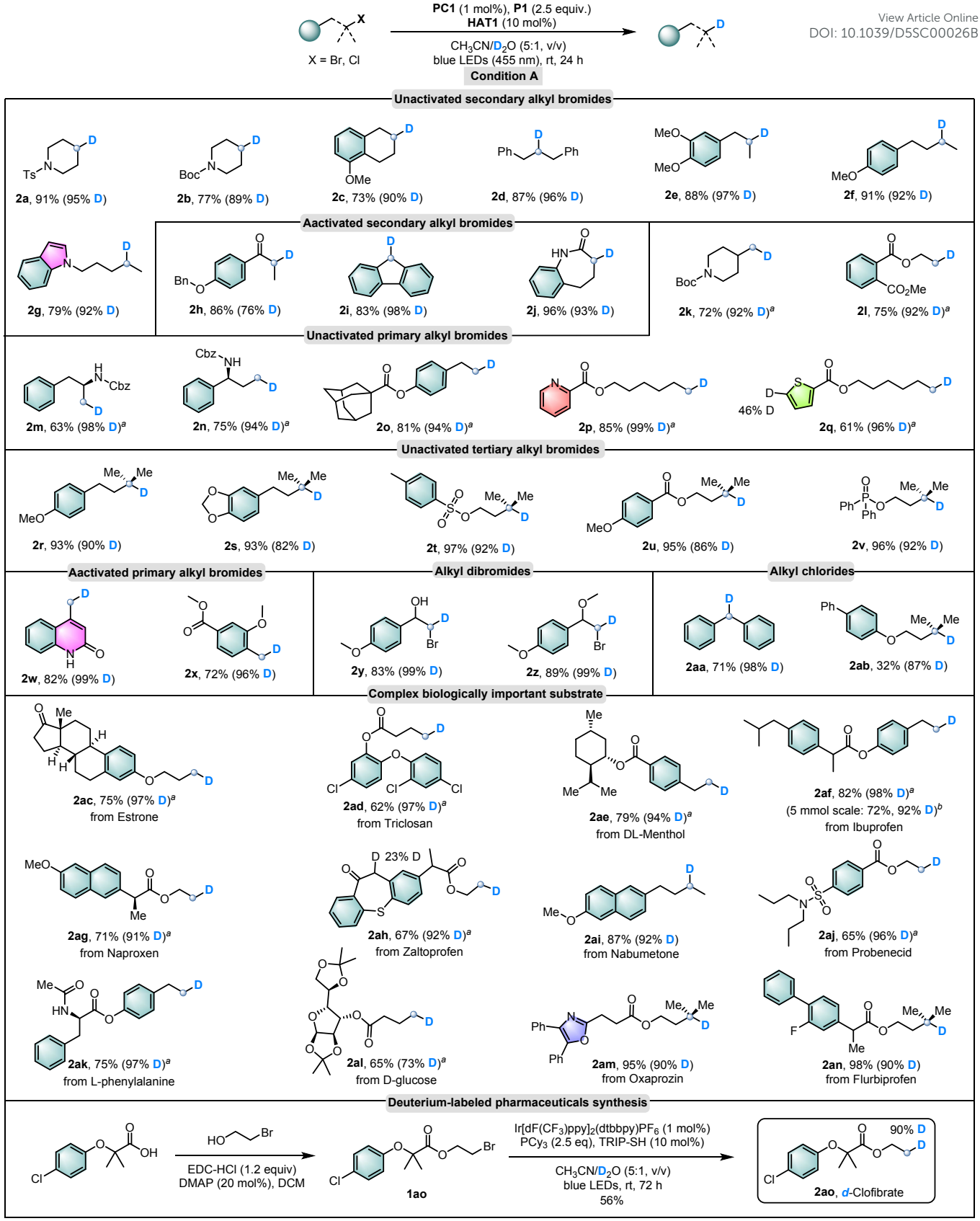

Scheme 2 Application of the XAT methodology in deuteration of alkyl halides. Reaction conditions: halides (0.20 mmol, 1.0 equiv.), **PC1** (0.002 mmol, 1 mol%), **P1** (0.50 mmol, 2.5 equiv.), **HAT1** (0.02 mmol, 10 mol%) in CH_3CN/D_2O (2.0 mL, v/v = 5:1, 0.1 M) at room temperature under Ar atmosphere, 455 nm LEDs (10 W), 24 h. Yields are of isolated products after chromatographic purification. PC = photocatalyst. HAT = hydrogen atom transfer. The D content was determined by ^1H NMR spectroscopy. [a] time = 48 h. [b] time = 72 h.

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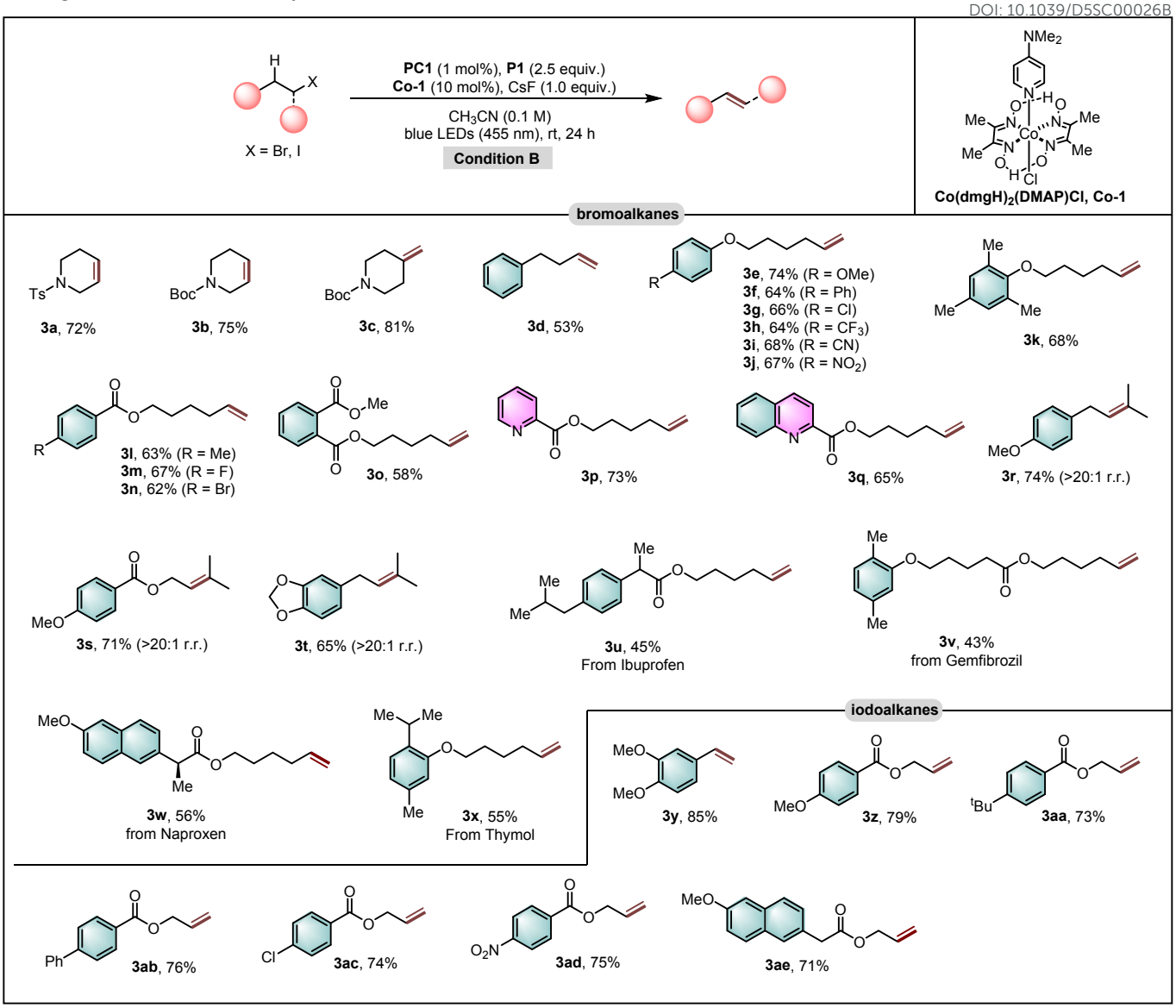
Dehalogenative elimination of alkyl halides



Scheme 3 Application of the XAT methodology in β-elimination of alkyl halides. Reaction conditions: halides (0.20 mmol, 1.0 equiv.), **PC1** (0.002 mmol, 1 mol%), **P1** (0.50 mmol, 2.5 equiv.), **Co-1** (0.02 mmol, 10 mol%), CsF (1.0 equiv.) in CH_3CN (0.1 M) at room temperature under Ar atmosphere, 455 nm LEDs (10 W), 24 h. Yields are of isolated products after chromatographic purification. PC = photocatalyst. Ts = *p*-toluenesulfonyl. Boc = *tert*-butoxycarbonyl.

After successful validation of dehalogenative deuteration via our XAT strategy, we envisioned that the synthesis of olefins based on a dual photoredox-cobalt catalytic cycle, using XAT mediated by phosphoranyl radicals as a blueprint for halide activation. We began our investigation by using alkyl bromide **1a** as the model substrate under 455 nm light irradiation. After careful optimization (SI, Table S6), the use of PC1 (1 mol%) as the photocatalyst, $Co(dmgH)_2(DMAP)Cl$ (Co-1, 10 mol %) as the commercially available cobaloxime, **P1** (2.5 equiv.) as the XAT reagent, and CsF as base in CH_3CN solvent under 455 nm light irradiation at room temperature, producing the product **3a** in 72% yield (Scheme 3). Subsequently, a wide range of terminal and symmetrical substrates were screened. *N*-Boc protected amine (**3b** and **3c**) were all well compatible with the modified reaction conditions, furnishing the desired olefins in 75% and 81% yields, respectively. The use of (4-bromobutyl)benzene as substrate was possible to generate the corresponding product **3d** in moderate yield. Moreover, the influence of electronic properties of aryl ethers on the phenyl rings was investigated, revealing that electron-withdrawing group (Cl, CF_3, CN, NO_2) or electron-donating group (Me, OMe) were compatible and showed little effect on the reaction, gave products **3e–3k** in 64–74% yields. Aryl esters are also suitable substrates, could successfully to generate the desired products **3l–3o** in 58–67% yields. Besides, heteroaromatic rings such as pyridine and quinoline were all showed good compatibility with the reaction system, generating **3p** and **3q** in acceptable yields. Notably, the use of tertiary alkyl bromide exhibited remarkable regioselectivity, yielding the internal olefins (**3r**-**3t**) in 65-74% yields. In addition, late-stage modification of drug molecules is the basis for the evaluation of a practical protocol. Alkyl bromides derived from complex molecules, such as ibuprofen (**3u**) gemfibrozil (**3v**),

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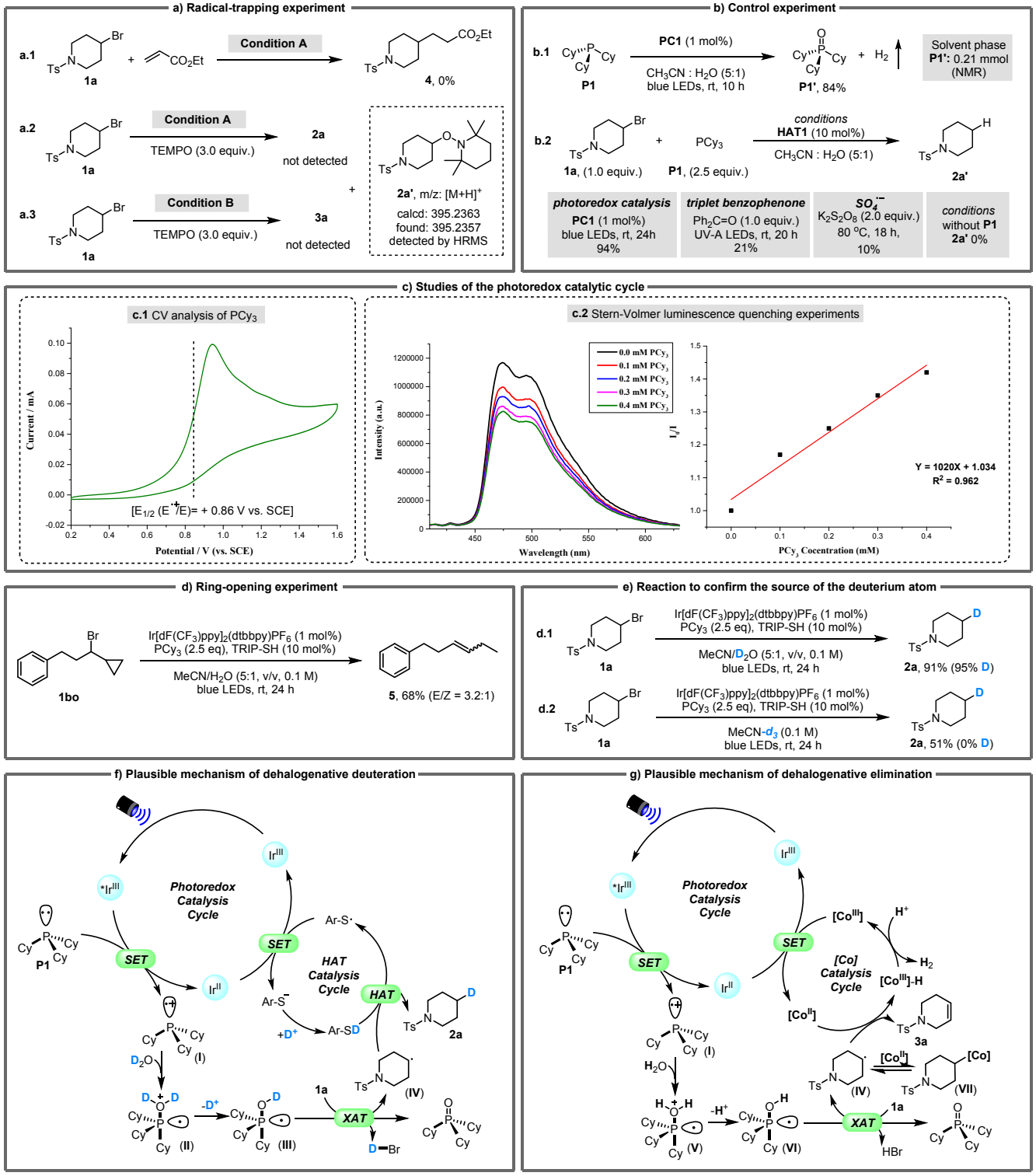
naproxen (**3w**), and thymol (**3x**) provided the desired terminal olefins in 43-56% yields. Furthermore, iodoalkanes could also be employed as viable substrates, and varied formation of the corresponding olefines was observed (**3y**-**3ae**).



Scheme 4 Mechanistic investigations. (a) Radical-trapping experiment. (b) Control experiment. (c) Studies of photoredox catalytic cycle. (d) Radical clock experiment. (e) Reaction to confirm the source of the deuterium atom. (f) Plausible catalytic cycle of dehalogenative deuteration. (g) Plausible catalytic cycle of dehalogenative elimination.

Next, in order to gain more insights into the reaction mechanism, we performed a series of mechanistic experiments. A Giese reaction was first conducted with **1a** and ethyl acrylate, but no desired product **4** was afforded under the condition A (Scheme 4a.1). Subsequently,

the addition of the radical scavenger TEMPO (2,2,6,6-tetramethylpiperidinooxy) led to significant inhibition of the desired reaction, indicating possible radical mechanism involvement, and the trapping product **2a'** was detected by HRMS analysis (Scheme 4a.2). The phosphoranyl radical intermediate can exhibit the reactivity of a 'free' hydrogen atom, which might be a suitable reagent to perform XAT process.[20] To experimentally validate the formation of 'free' hydrogen atom from the phosphoranyl radical intermediate, tricyclohexylphosphane (PCy_3)-mediated hydrogen evolution was investigated. To our delight, combined with **PC1** as photocatalyst and H_2O as the hydrogen source in acetonitrile under irradiation with blue LEDs, the generation of H_2 was experimentally verified in solution phase. At the same time, tricyclohexylphosphine oxide was provided as the by-product (Scheme 4b.1). Furthermore, to explore the importance of this PR_3–OH radical intermediate in XAT process, we chose the dehalogenation of 4-bromo-1-tosylpiperidine **1a**, using PCy_3 as the XAT-agent precursor and 2,4,6-triisopropylbenzenethiol (**HAT1**)-H_2O as the H-atom donor (Scheme 4b.2). The generation of R_3P-OH radical intermediate via photochemical or thermal modes through single electron transfer (SET) followed by deprotonation. The debromination product **2a'** was obtained by the combination of PCy_3 and single electron oxidants (**PC1**, benzophenone, and $K_2S_2O_8$). When **P1** was not involved in these cases, no product was observed, indicating that the PR_3–OH radical was an indispensable intermediate in the dehalogenation process.

Cyclic voltammetry (CV) experiments and analyses were carried out, the potential of PCy_3 was measured (half-wave potential $E_{1/2}$ ($E^{+\cdot}$/E) = +0.86 V vs saturated calomel electrode (SCE) in MeCN. The photocatalyst **PC1** [$E_{1/2}$ ($^*Ir^{III}/Ir^{II}$) = + 1.21 V vs SCE][21] has higher oxidation potential to oxidize PCy_3 (Scheme 4c.1). In addition, Stern–Volmer quenching studies were then conducted, which revealed that PCy_3 quenches the photoexcited **PC1** (Scheme 4c.2). α-Bromocyclopropane **1bo** was chosen to be used as a radical clock, and the resulting ring-opening product **5** was formed in 68% yield, which strongly support the radical dehalogenation involved in this process (Scheme 4d). Finally, the deuterium labeling experiments conducted with D_2O and MeCN-d_3 as the potential deuterium source demonstrated that the deuterium atom should come from D_2O, and CH_3CN was not act as a hydrogen atom donor (Scheme 4e). This result indicated that the extra water has a great effect on the D-incorporation.

Based on these experimental results and literature reports,[20] two feasible reaction mechanisms are separately proposed in Scheme 4. For the mechanism of dehalogenative deuteration of halides (Scheme 4f), we postulated that the photoexcited complex $^*[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (***PC1**, $^*E_{red}$ = +1.21 V versus SCE) oxidizes **P1** to generated a radical cation intermediate (**I**), at the same time, Ir^{III} was reduced to Ir^{II} species. This radical cation reacts with D_2O to form a radical cation intermediate (**II**), which, after subsequent deprotonation, furnishes the key Cy_3P-OD radical intermediate (**III**). This highly reactive radical cation undergoes XAT with 4-bromo-1-tosylpiperidine **1a**, and the resulting nucleophilic alkyl radical (**IV**) can readily undergo HAT from the 2,4,6-triisopropylbenzenethiol (**HAT1**, S-H BDE = 80 kcal·mol^{-1})[12d] to provide the deuterated product **2a** and the ArS• radical intermediate (Ar = 2,4,6-triisopropylphenyl). Lastly, ArS• oxidizes Ir^{II} to ground-state Ir^{III} to complete the photoredox cycle, and the generated ArS^- abstracts one deuteron from D_2O or radical intermediate (**II**) to restart the thiol catalysis. For the mechanism of dehalogenative Eelimination of alkyl halides (Scheme 5g), reductive quenching of a photoexcited complex ***PC1** by **P1** would generate a radical cation intermediate (**I**) and reducing Ir^{II} species. The intermediate (**I**) capture H_2O in CH_3CN, followed by deprotonation in the presence of base to produce the key radical intermediate (**VI**). At this point, XAT process between intermediate (**VI**) and the alkyl halide (e.g., with 4-bromo-1-tosylpiperidine **1a**) should generate the alkyl radical (**IV**), which can be captured by [Co(II)] species lead to [Co(III)]−alkyl intermediate (**VII**),[22] then β-hydride elimination from **(VII)** would give the olefin product **3a** and [Co(III)]-H species. Finally, [Co(III)]-H species react with H^+ to evolve H_2 and deliver [Co(III)] species that can close the cobalt cycle by oxidize Ir^{II}, meanwhile, Ir^{II} back to Ir^{III} to complete the photoredox cycle. Alternatively, other mechanism based on the direct HAT of the [Co(II)] species with the alkyl radical (**IV**),[23] may lead to the same result.

Conclusions

In summary, we have developed a photocatalytic, phosphine-mediated strategy for the dehalogenative deuteration of unactivated alkyl halides, utilizing D_2O as an inexpensive and safe deuterium source under mild conditions. This study demonstrates the effective conversion of a wide range of unactivated primary, secondary, and tertiary alkyl bromides and chlorides into deuterated products, achieving good to excellent yields and high level of deuterium incorporation. Notably, the successful gram-scale experiments and late-stage deuteration of complex natural products and drug derivatives underscore the potential applicability of our method. Additionally, our C-X bond activation strategy allows for the dehalogenative elimination of unactivated alkyl halides. We believe this protocol offers an efficient tool for photochemical transformations.

Author contributions

W.S. and L.G. conceived the concept. W.S. and B.G. performed and analyzed the experiments. J.T. and C.Y. contributed to the data analysis. W.S. and L.G. wrote the manuscript. Y.Z. and W.X. supervised and directed the project.

Conflicts of interest

There are no conflicts to declare.

Data availability

All data supporting the findings including the experimental procedures and characterization of compounds are available within the article and its Supporting Information.

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Data availability statements

All data supporting the findings including the experimental procedures and characterization of compounds are available within the article and its Supporting Information.

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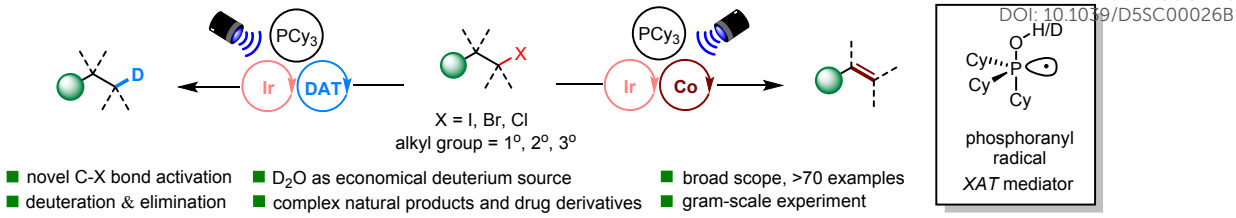

A photocatalytic phosphine-mediated strategy for the dehalogenative deuteration of unactivated alkyl halides is herein reported.