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# 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 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<sub>2</sub>O as an economical source of deuterium. The use of Cy<sub>3</sub>P 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 also be achieved by integrating photoredox and cobalt catalysis using the same halogen-atom transfer agents.

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## Introduction

Deuterium-labeled compounds play a significant role in organic synthesis and pharmaceutical chemistry.<sup>1</sup> 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.<sup>2</sup> 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).<sup>3</sup> 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.<sup>4</sup> However, this methodology still faces significant limitations, such as low

deuterium incorporation and unsatisfactory regioselectivity. Dehalogenative deuteration of 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.<sup>5</sup>

Organic halides are important and versatile compounds, but their use in photoredox chemistry is limited by their highly negative reduction potentials ( $E_{\text{red}} \leq 2.0$  V vs. SCE for unactivated alkyl iodides).<sup>6</sup> In recent years, the development of halogen-atom transfer (XAT) processes has made significant strides in generating carbon radicals for synthetic chemistry.<sup>7</sup> 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 diiodination of alkyl iodides using Et<sub>3</sub>B as the XAT reagent (Scheme 1b(i)).<sup>8</sup> Leonori and Juliá demonstrated that strongly nucleophilic  $\alpha$ -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)).<sup>9</sup> More recently, Lee *et al.* reported a thiyl radical-catalyzed deuterative debromination reaction of alkyl and aryl bromides using a stoichiometric amount of (TMS)<sub>3</sub>SiH as the XAT reagent (Scheme 1b(iii)).<sup>10</sup> Despite the advantages demonstrated by these XAT-mediated transformations, the development of general and robust

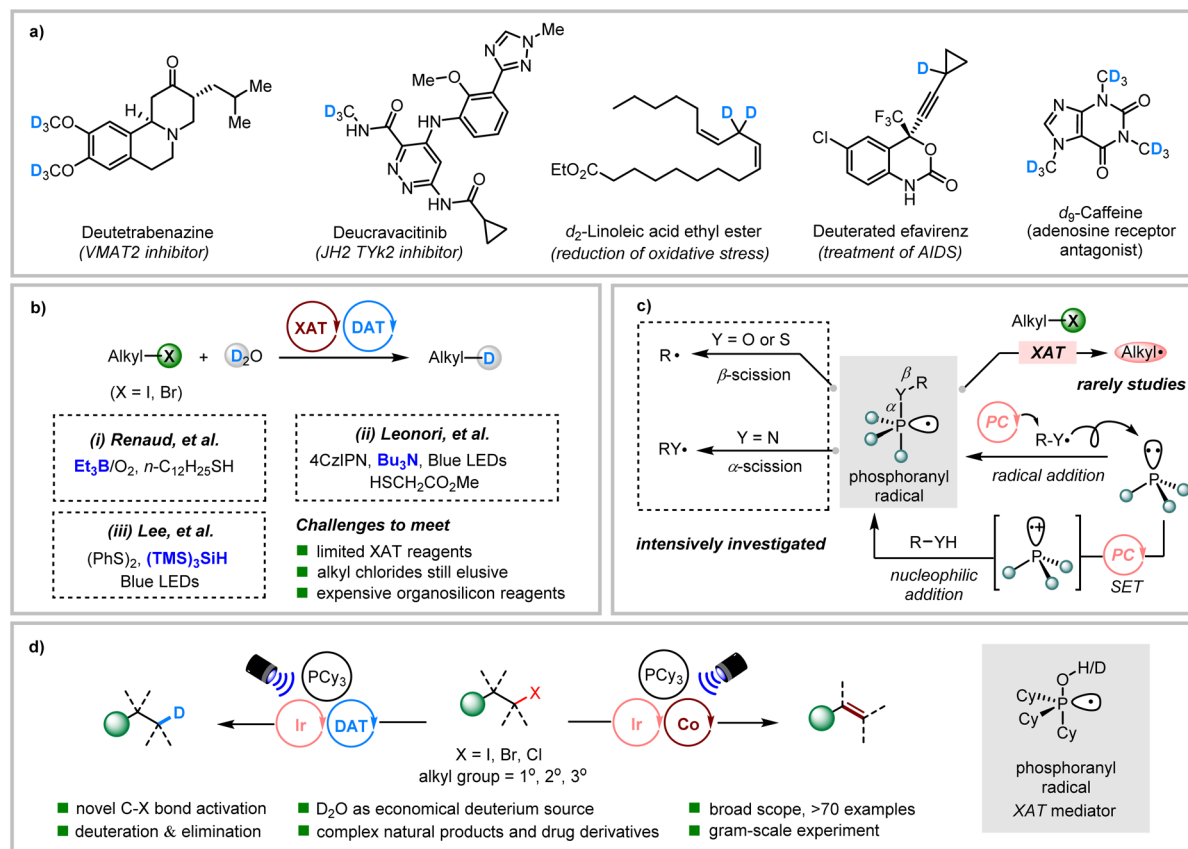
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**Scheme 1** Dehalogenative deuteration via halogen atom transfer. (a) Several representative deuterated drugs. (b) Current status for deuteration of alkyl halides via XAT. (c) Application of phosphoranyl radicals in organic synthesis. (d) This work: phosphoranyl radical mediated C(sp<sup>3</sup>)-halogen activation via XAT process.

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.<sup>11</sup> With the advent of visible light catalysis, phosphoranyl radicals can be generated under 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  $\beta$ -scission has been extensively investigated.<sup>12</sup> More recently, Doyle *et al.* achieved the homolytic cleavage of the P–N bond via  $\alpha$ -scission to facilitate the hydroamination of olefins with primary sulfonamides or azoles.<sup>13</sup> 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.<sup>14</sup> The highly nucleophilic nature of phosphoranyl radicals<sup>15</sup> may lead to kinetic polar effects that enhance the XAT process.

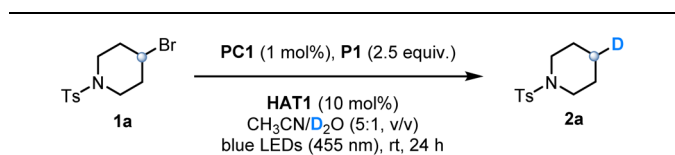
Herein, we report an unprecedented photocatalytic deuterodehalogenation of unactivated alkyl halides using photoredox and thiol organocatalysis, with PCy<sub>3</sub> serving as the halogen-

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 deuterodehalogenation 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,<sup>16</sup> 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



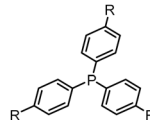
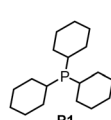
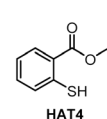
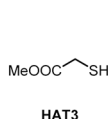
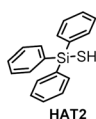
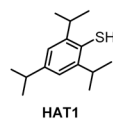
Table 1 Optimization studies<sup>a</sup>

Entry	Variation of standard conditions	Yield <sup>b</sup> (%)	D-inc. <sup>c</sup> (%)
1	None	91	95
2	<b>P2</b> instead of <b>P1</b>	25	90
3	<b>P3</b> instead of <b>P1</b>	<5	—
4	No <b>P1</b>	N.D.	—
5	<b>HAT2</b> instead of <b>HAT1</b>	62	94
6	<b>HAT3</b> instead of <b>HAT1</b>	81	91
7	<b>HAT4</b> instead of <b>HAT1</b>	88	87
8	<b>PC2</b> instead of <b>PC1</b>	79	93
9	<b>PC3</b> instead of <b>PC1</b>	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 <b>HAT1</b>	35	95

**PC1**: [Ir(dF(CF<sub>3</sub>)ppy)<sub>2</sub>(dtbbpy)]PF<sub>6</sub>  
Ir<sup>III</sup>/Ir<sup>IV</sup> = +1.21 V vs SCE

**PC2**: [Ir(dF(CF<sub>3</sub>)ppy)<sub>2</sub>(bpy)]PF<sub>6</sub>  
Ir<sup>III</sup>/Ir<sup>IV</sup> = +0.97 V vs SCE

**PC3**: [Ir(dF(CF<sub>3</sub>)ppy)<sub>2</sub>(4,4'-dCF<sub>3</sub>bpy)]PF<sub>6</sub>  
Ir<sup>III</sup>/Ir<sup>IV</sup> = +1.65 V vs SCE



<sup>a</sup> 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<sub>3</sub>CN/D<sub>2</sub>O (2.0 mL, v/v = 5 : 1, 0.1 M) at room temperature under an Ar atmosphere, 455 nm LEDs (10 W), 24 h. <sup>b</sup> Yields are of isolated products after chromatographic purification. <sup>c</sup> D-inc. determined by <sup>1</sup>H NMR. Ts = *p*-toluenesulfonyl, PC = photocatalyst, HAT = hydrogen atom transfer, D-inc. = deuterium incorporation, N.D. = not detected.

deuterodehalogenation could not occur in the absence of the 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 ESI, Table S2†), we found that photocatalysts with excited state oxidation potentials below that of PCy<sub>3</sub> were ineffective for the reaction. Ir-based photocatalysts (**PC2**) were explored but 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).

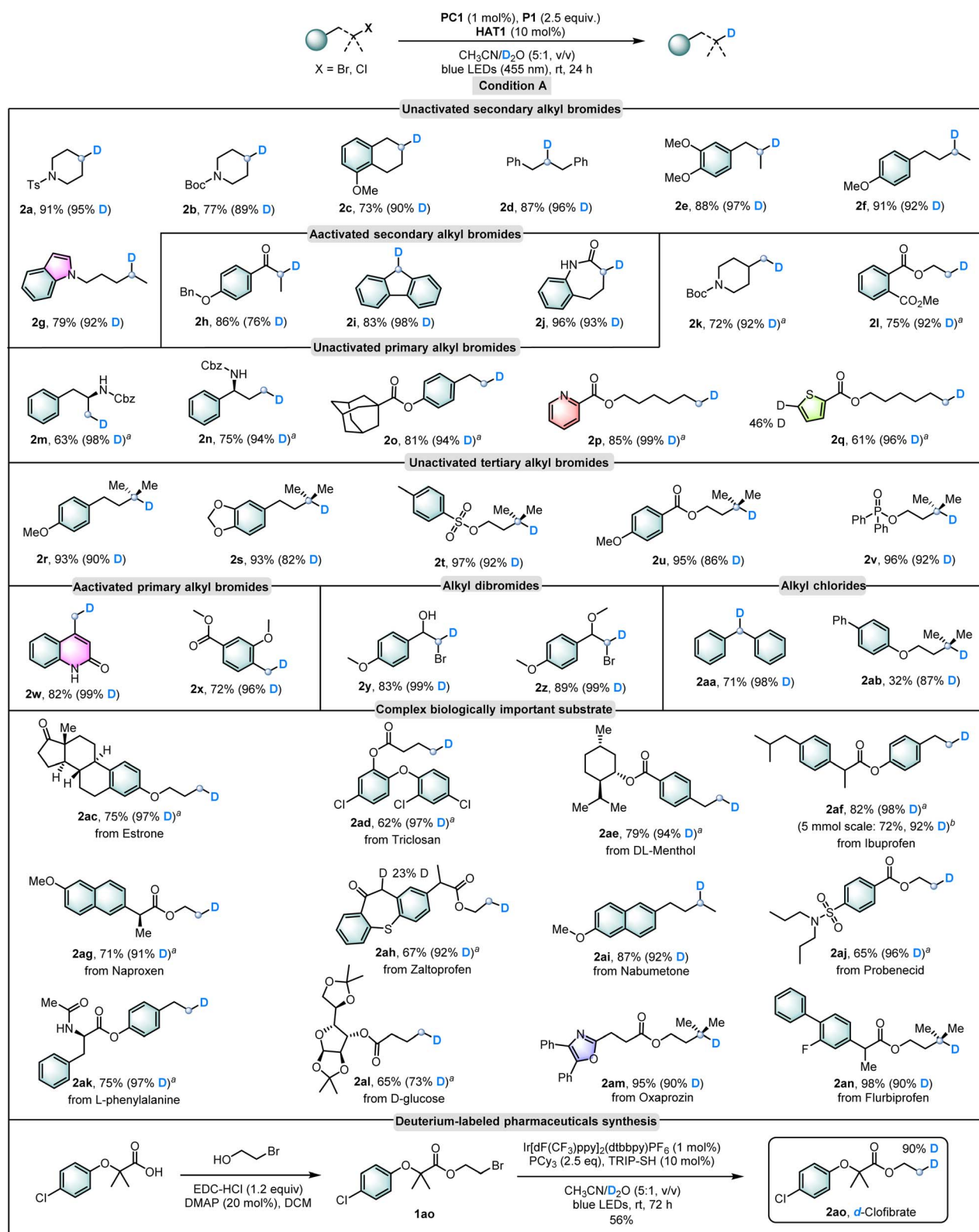
### Dehalogenative deuteration of alkyl halides

Under the existing optimized conditions, we investigated the scope of deuterodehalogenation with respect to alkyl halides, as shown in Scheme 2. It is noteworthy to mention 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 were first investigated. In most cases, good yields, and high levels of D-incorporation of the products (73–91 yields, 89–97% D-inc.) were obtained. Cyclic bromides were found to be suitable C(sp<sup>3</sup>)-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,<sup>17</sup> 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. The dibromomethylene unit was then subjected to test the adaptability of our XAT method, furnishing the desired mono-deuterated 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 practicality of the method, late-stage deuteration of complex molecules was conducted using our XAT strategy. The deuterodehalogenation of pharmaceutical 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





**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<sub>3</sub>CN/D<sub>2</sub>O (2.0 mL, v/v = 5 : 1, 0.1 M) at room temperature under an 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 <sup>1</sup>H NMR spectroscopy. <sup>a</sup>Time = 48 h. <sup>b</sup>Time = 72 h.



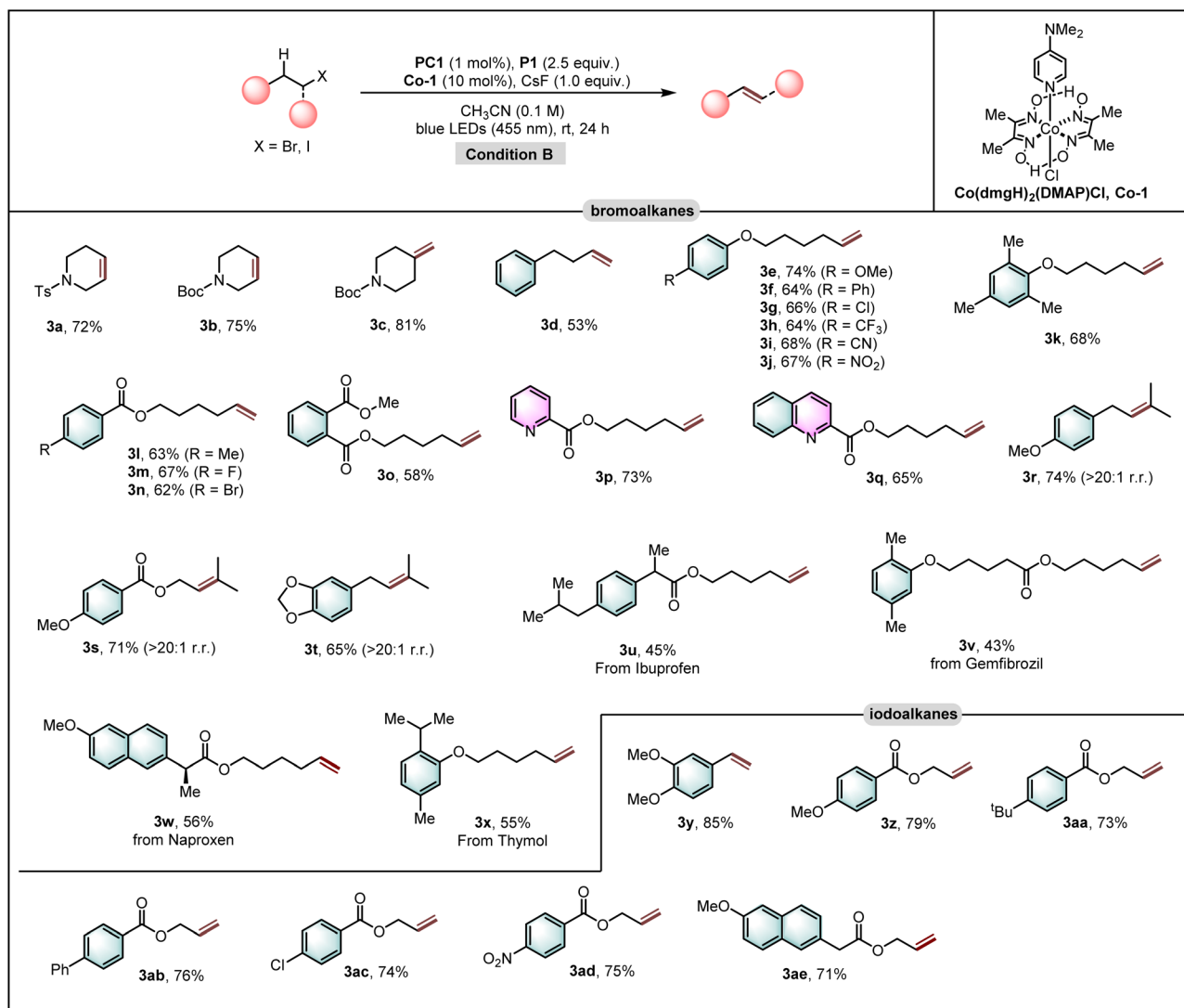


products in 75% and 65% yields. Furthermore, the generality and practicality of this strategy to tertiary bromides can be further extended to complex pharmaceuticals (**2am** and **2an**). The incorporation of a deuterium atom to parent drugs and drug candidates can dramatically enhance the metabolism and pharmacokinetic properties, without altering their desired traits.<sup>18</sup> Clofibrate is a lipid-lowering drug that is also effective in the treatment of neonatal jaundice.<sup>19</sup> Utilizing our strategy, deuterated clofibrate (**2ao**) was smoothly achieved from commercially available clofibric acid.

### Dehalogenative elimination of alkyl halides

After successful validation of dehalogenative deuteration *via* our XAT strategy, we envisioned 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 (ESI, Table S6<sup>†</sup>), the use of **PC1** (1 mol%) as the photocatalyst, **Co(dmgH)<sub>2</sub>(DMAP)Cl** (**Co-1**, 10 mol%) as the commercially available cobaloxime, **P1** (2.5 equiv.) as the XAT reagent, and CsF as the base in CH<sub>3</sub>CN solvent under 455 nm light irradiation at room temperature produced the product **3a** in 72% yield (Scheme 3). Subsequently, a wide range of terminal and symmetrical substrates were screened. *N*-Boc protected amines (**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 the substrate generated 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 groups (Cl, CF<sub>3</sub>, CN, NO<sub>2</sub>) or electron-donating groups (Me, OMe) were compatible and showed little

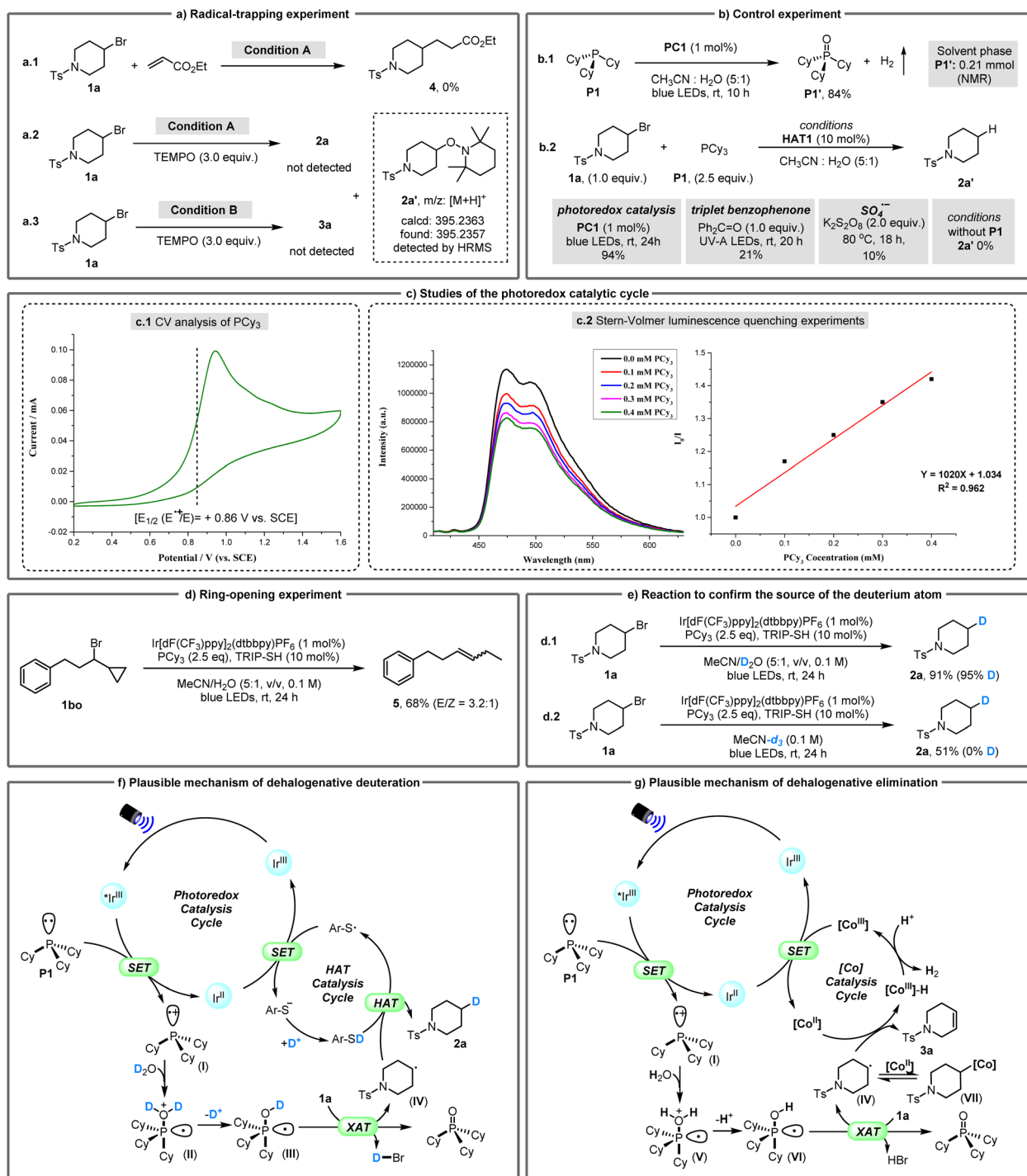


**Scheme 3** Application of the XAT methodology in  $\beta$ -elimination of alkyl halides. Reaction conditions: halides (0.20 mmol, 1.0 equiv.), **PC1** (0.002 mmol, 1 mol%), **P1** (0.50 mmol, 2.5 equiv.), **Co-1** (0.02 mmol, 10 mol%), CsF (1.0 equiv.) in CH<sub>3</sub>CN (0.1 M) at room temperature under an 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.



effect on the reaction, giving products **3e–3k** in 64–74% yields. Aryl esters are also suitable substrates, and could successfully generate the desired products **3l–3o** in 58–67% yields. Besides, heteroaromatic rings such as pyridine and quinoline 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**), naproxen (**3w**), and thymol (**3x**), provided the desired terminal olefins in 43–56% yields. Furthermore, iodoalkanes could also be



**Scheme 4** Mechanistic investigations. (a) Radical-trapping experiment. (b) Control experiment. (c) Studies of the 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.



employed as viable substrates, and varied formation of the corresponding olefins was observed (**3y–3ae**).

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 condition A (Scheme 4a.1). Subsequently, the addition of the radical scavenger TEMPO (2,2,6,6-tetramethylpiperidinoxy) 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 the XAT process.<sup>20</sup> To experimentally validate the formation of a 'free' hydrogen atom from the phosphoranyl radical intermediate, tricyclohexylphosphane (PCy<sub>3</sub>)-mediated hydrogen evolution was investigated. To our delight, combined with **PC1** as the photocatalyst and H<sub>2</sub>O as the hydrogen source in acetonitrile under irradiation with blue LEDs, the generation of H<sub>2</sub> was experimentally verified in the 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<sub>3</sub>–OH radical intermediate in the XAT process, we chose the dehalogenation of 4-bromo-1-tosylpiperidine **1a**, using PCy<sub>3</sub> as the XAT-agent precursor and 2,4,6-triisopropylbenzenethiol (**HAT1**)–H<sub>2</sub>O as the H-atom donor (Scheme 4b.2). The generation of the R<sub>3</sub>P–OH radical intermediate occurred *via* photochemical or thermal modes through single electron transfer (SET) followed by deprotonation. The debromination product **2a'** was obtained by the combination of PCy<sub>3</sub> and single electron oxidants (**PC1**, benzophenone, and K<sub>2</sub>S<sub>2</sub>O<sub>8</sub>). When **P1** was not involved in these cases, no product was observed, indicating that the PR<sub>3</sub>–OH radical was an indispensable intermediate in the dehalogenation process.

Cyclic Voltammetry (CV) experiments and analyses were carried out, and the potential of PCy<sub>3</sub> was measured (half-wave potential  $E_{1/2}$  ( $E^+/E$ ) = +0.86 V *vs.* saturated calomel electrode (SCE)) in MeCN. The photocatalyst **PC1** [ $E_{1/2}$  (\*Ir<sup>III</sup>/Ir<sup>II</sup>) = +1.21 V *vs.* SCE]<sup>21</sup> has a higher oxidation potential to oxidize PCy<sub>3</sub> (Scheme 4c.1). In addition, Stern–Volmer quenching studies were then conducted, which revealed that PCy<sub>3</sub> quenches the photoexcited **PC1** (Scheme 4c.2).  $\alpha$ -Bromocyclopropane **1b** was chosen to be used as a radical clock, and the resulting ring-opening product **5** was formed in 68% yield, which strongly supports the radical dehalogenation involved in this process (Scheme 4d). Finally, the deuterium labeling experiments conducted with D<sub>2</sub>O and MeCN-d<sub>3</sub> as the potential deuterium source demonstrated that the deuterium atom should come from D<sub>2</sub>O, and CH<sub>3</sub>CN did 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,<sup>20</sup> 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(dFCF<sub>3</sub>ppy)<sub>2</sub>(dtbbpy)]PF<sub>6</sub> (\***PC1**, \* $E_{red}$  = +1.21 V *versus* SCE) oxidizes **P1** to generate a radical cation intermediate

(**I**), at the same time, Ir<sup>III</sup> was reduced to Ir<sup>II</sup> species. This radical cation reacts with D<sub>2</sub>O to form a radical cation intermediate (**II**), which, after subsequent deprotonation, furnishes the key C<sub>3</sub>P–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 with 2,4,6-triisopropylbenzenethiol (**HAT1**, S–H BDE = 80 kcal mol<sup>−1</sup>)<sup>12d</sup> to provide the deuterated product **2a** and the ArS<sup>•</sup> radical intermediate (Ar = 2,4,6-triisopropylphenyl). Lastly, ArS<sup>•</sup> oxidizes Ir<sup>II</sup> to ground-state Ir<sup>III</sup> to complete the photoredox cycle, and the generated ArS<sup>−</sup> abstracts one deuteron from D<sub>2</sub>O or radical intermediate (**II**) to restart the thiol catalysis. For the mechanism of dehalogenative elimination of alkyl halides (Scheme 4g), reductive quenching of a photoexcited complex \***PC1** by **P1** would generate a radical cation intermediate (**I**) and reduced Ir<sup>II</sup> species. The intermediate (**I**) captures H<sub>2</sub>O in CH<sub>3</sub>CN, followed by deprotonation in the presence of a base to produce the key radical intermediate (**VI**). At this point, the 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(III)] species, leading to the [Co(III)]–alkyl intermediate (**VII**),<sup>22</sup> then  $\beta$ -hydride elimination from (**VII**) would give the olefin product **3a** and [Co(III)]–H species. Finally, [Co(III)]–H species react with H<sup>+</sup> to evolve H<sub>2</sub> and deliver [Co(III)] species that can close the cobalt cycle by oxidizing Ir<sup>II</sup>, meanwhile, Ir<sup>II</sup> converts back to Ir<sup>III</sup> to complete the photoredox cycle. Alternatively, another mechanism based on the direct HAT of the [Co(III)] species with the alkyl radical (**IV**)<sup>23</sup> 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<sub>2</sub>O 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 a 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.

## Data availability

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

## 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.

## Acknowledgements

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