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Pd-catalyzed deuteration of aryl halides with deuterium oxide

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Late-stage deuteration of aryl halides with deuterium oxide is a highly desirable but challenging transformation, primarily due to the difficulty of activating inert carbon-halogen bonds and the umpolung of deuterium oxide in the presence of various functional groups. To achieve this transformation, efforts have been made to develop photo-chemical, electro-chemical, or mechano-chemical strategies. However, these approaches often require specialized setups or activated substrates. Despite the well-known functional group tolerance of palladium catalysis, which makes it valuable in late-stage functionalization, a palladium-catalyzed deuteration of aryl halides with deuterium oxide has remained elusive. Herein, a deuteration reaction of aryl bromides, chlorides, and triflates with deuterium oxide has been developed, through palladium catalysis. Chemical equivalent amount of D_2O is required for inert substrates like aryl chlorides. The reaction features high functional group tolerance, making it suitable for late-stage deuteration.

In 2024, the FDA approved an additional deuterated drug for medical use[1], with at least ten other deuterated drugs currently in clinical or preclinical trials[2]. Deuterium on the drug molecules can significantly lower metabolism rates and reduce the dosing frequency because of kinetic isotope effect[3–5]. Consequently, the deuterium labeling technology has been recognized as a crucial tool to enhance the pharmacokinetic and pharmacodynamics properties of drug molecules[6,7]. As a result, the development of late-stage deuteration methodologies[8–11] is important in drug discovery area. Catalytic deuteration of aryl (pseudo)halides is a highly desirable transformation because various aryl (pseudo)halides are easy to prepare from pharmaceuticals[12–15], and thousands of aryl (pseudo)halides drug intermediates are commercially available. According to stoichiometric calculations, catalytic deuteration of aryl halide requires a deuteride donor. Deuterium sources[8,16–31] successfully applied to the deuteration of aryl halides include $NaBD_4$[16], DCOOK[16,17], D_2[18,19],PrOD-d_8[20,21], MeOD-d_4[22], CD_3CN[23], D_2O[24–27], etc. Among these, D_2O is the most cost-effective commercially available deuterium source (Fig. 1a)[8]. However, current late-stage deuteration reaction of aryl halides with D_2O still require special reaction setups for reduction, or high deuterium source loading[24–27]. Herein, a general palladium-catalyzed deuteration reaction of aryl halides with deuterium oxide has been developed, where deuterium oxide effectively serves as the deuteride source under cross-coupling conditions.

Traditional deuteration strategies of aryl halides require the preparation of stoichiometric organometallic carbanion reagents, such as organolithium or Grignard reagents[24]. These organometallic carbanion reagents, when quenched with D_2O, yield deuterated products. However, the presence of various functional groups leads to side reactions with the stoichiometric carbanion reagents, complicating the application of the strategy in late-stage functionalization[32–36]. To address the limitation, the Liu group developed a KOMe/$Me_3SiSiMe_3$ system, which may form transient carbanions from aryl halides and then trapped by the large excess of CD_3CN to provide the desired deuterated product[23]. To further investigate the use of D_2O as a deuterium source for late-stage aryl halide deuteration, the Gong group explored a photochemical approach, while the Lei group developed an electrochemical strategy. However, both methods require D_2O to be used in large excess or as a co-solvent (Fig. 1b)[25,26]. The Lian group developed a mechanochemical strategy to achieve deuteration reaction of aryl iodides with 2–4 equivalents of D_2O[27]. However, more inert aryl bromides or aryl chlorides substrates have not been successfully applied

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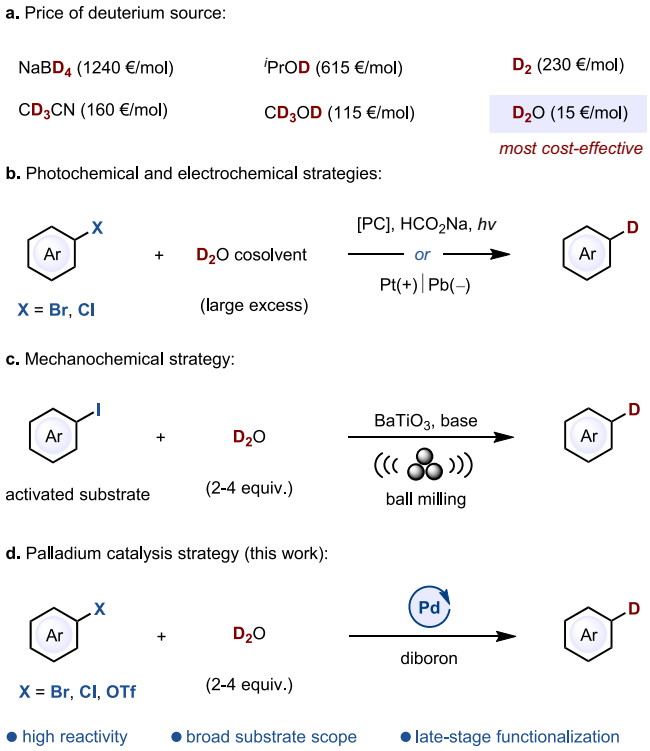

Fig. 1 | Deuteration of aryl halides with D_2O. a Comparison of the costs of deuterium sources. **b** Photochemical and electrochemical strategies. **c** Mechanochemical strategy. **d** This work: Palladium catalysis strategy.

in the strategy (Fig. 1c). Surprisingly, despite decades of extensive development of palladium-catalyzed cross-coupling reactions, which are known for their high reactivity, excellent functional group tolerance, and broad substrate scope[37–42], a palladium-catalyzed deuteration of aryl halides with deuterium oxide has not yet been achieved[43,44]. Herein, a palladium-catalyzed deuteration reaction of various aryl (pseudo)halides with D_2O has been developed (Fig. 1d). The reaction exhibits chemical equivalent amount of D_2O loading and broad substrate scope. The high functional group tolerance of the transformation enables the late-stage functionalization of several drug molecules.

Results

Optimization of reaction conditions

We propose that the success of a palladium-catalyzed deuteration of aryl halides with D_2O lies in an efficient catalytic umpolung reaction of deuterium oxide, followed by a cross-coupling between aryl halide and the in-situ generated deuteride source. The Zhu group has reported that the combination of diboron and water can be used as a hydride donor in a reductive Heck reaction[45]. Inspired by the work, we propose that, in the presence of diboron, a palladium catalyst may facilitate an efficient umpolung reaction of deuterium oxide to generate the deuteride source, rather than engaging in direct transmetallation with diboron to produce the borylation product. The unusual selectivity for the transmetallation step may provide us a chance to achieve the challenging deuteration reaction of aryl halides with heavy water.

The deuteration reaction of 4-fluorobromobenzene (**1a**), with deuterium oxide as the deuterium source, was selected as the model reaction, because the yield and deuterated ratio of fluorobenzene (**2a**) could be easily determined with ^{19}F NMR. The selectivity of deuteration and borylation is controlled by the structures of aryl palladium intermediate and diboron. Traditional basic cross-coupling reaction conditions can produce Ar-[Pd]-OR intermediates that coordinate with the Lewis acidic boron center of diboron, leading to borylation product (Table 1, entry 1–2). However, for the cationic palladium Ar-$[Pd]^+$, it is a different mechanism. The coordination of the cationic species with the Lewis acidic boron center is difficult, while facilitating the hydride coordination, even the in-situ generated hydride could be in low concentration. Generation of the Ar-$[Pd]^+$ intermediate from the Ar-[Pd]-Br intermediate necessitates a halide scavenger[46,47]. However, traditional silver salt halide scavenger[48,49] could oxidize diboron reagents and are incompatible with the palladium-hydride intermediate (Table 1, entry 3). In reported methods for halide-scavenger-mediated deuteration reaction, zinc salt was found to be the privileged additive to promote the transmetallation step without side reactions[46,47]. A variety of zinc salts have been tested, with zinc oxide showing the highest efficiency (Table 1, entry 4–7). Screening of diboron additives shows that diboron reagents with less steric hindrance such as B_2eg_2 or B_2cat_2 are more effective for the deuteration reaction (Table 1, entry 8–10). Commercially available palladium catalysts $Pd(^tBu_3P)_2$ and SPhos Pd G3 exhibit high efficiency with aryl halide substrates[50–52]. Various other palladium catalysts have been tested but demonstrated much lower yields (Table 1, entry 11–14, Supplementary Information Table S1). Reducing the temperature to room temperature but elongation of the reaction time shows similar results (Table 1, entry 15). Although the reactions of aryl bromide with diboron in the presence of a palladium catalyst are typically considered as borylation conditions, a deuteration product **2a** was obtained in 92% yield and 93% deuterated ratio when halide-scavenger-mediated conditions were applied.

Substrate scope

With the optimized reaction conditions in hand, the substrate scope of the deuteration reaction was explored (Fig. 2). The reaction exhibits a broad substrate scope and good functional group tolerance under the optimized reaction conditions. Heteroatom-containing rings such as dibenzothiophene, morpholine, carbazole, and thiophene rings are well-tolerated (**2c, 2d, 2e, 2h**, and **2u**). Coordinative *N*-heterocycles, such as pyrimidine, also show compatibility (**3h**). Substrates with ketone, trifluoromethyl, halogens, ester, aldehyde, sulfone, amide, imide, cyanide, and carbamate groups are all successfully deuterated (**2k, 2l, 2m, 2o, 2q, 2r, 2s**, and **2w**), which further broaden the substrate scope of the deuteration reactions. Late-stage modification of pharmaceutical compounds containing C–X bonds leads to the analogs of many drug molecules (**2t-2w, 3j**). Aryl chlorides, as well as heteroaryl chlorides (**3a-3j**), are all suitable substrates for the deuteration reactions when pre-catalyst AdBrettPhos Pd G3[53] and B_2eg_2 were applied (Supplementary Information Table S1). The results are consistent with a facile oxidative addition even for inert C–Cl bonds. Aryl triflates are also suitable substrates for the deuteration reactions (**4a-4j**). The oxidative addition of palladium(0) to aryl triflate leads to Ar-[Pd]-OTf, which does not involve coordinating halide species, eliminating the need for a halide scavenger such as ZnO (Supplementary Information Table S2). In comparison to other deuteration reactions of aryl (pseudo)halides with D_2O, the deuteration of aryl triflate substrates has not been reported with previous transition-metal-free methods. The results emphasize the broad substrate scope associated with palladium catalysis, distinguishing it from other strategies.

To further demonstrate the utility of the deuteration strategy, several deuterium-labeled drug molecules were synthesized using current methodology (Fig. 3). Drug molecules, such as naproamide and ipriflavon, could be easily halogenated in the presence of NBS or NCS[12–15]. Under standard conditions, the halogenated derivatives could be successfully transformed to the deuterated product [^{2}H]-napropamide (**2x**), [^{2}H]-aniracetam (**2 y**), [^{2}H]-clotrimazole (**2z**), and [^{2}H]-ipriflavone (**3k**) in high yields and high deuterated ratios. Many aromatic drug molecules metabolize to their phenolic forms because cytochrome P450 enzymes (CYPs) catalyze electrophilic hydroxylation of

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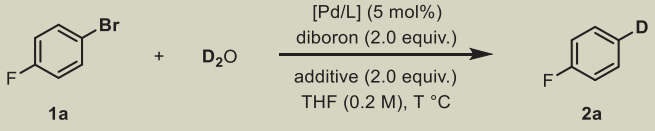
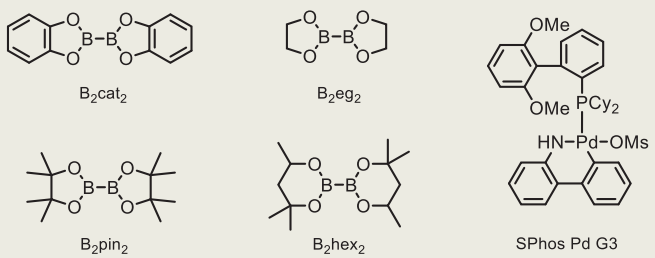
Table 1 | Reaction condition optimization



entry	Pd/L	diboron	additive	T (°C)	yield (%)	D (%)
1	$Pd(^tBu_3P)_2$	B_2cat_2	^{t}BuOK	70	43	42
2	$Pd(^tBu_3P)_2$	B_2cat_2	DABCO	70	43	65
3	$Pd(^tBu_3P)_2$	B_2cat_2	AgOTf	70	<5	--
4	$Pd(^tBu_3P)_2$	B_2cat_2	$Zn(BF_4)_2{\cdot}H_2O$	70	47	17
5	$Pd(^tBu_3P)_2$	B_2cat_2	$Zn(OTf)_2$	70	58	50
6	$Pd(^tBu_3P)_2$	B_2cat_2	$Zn(OAc)_2$	70	56	71
7	$Pd(^tBu_3P)_2$	B_2cat_2	ZnO	70	89	89
8	$Pd(^tBu_3P)_2$	B_2eg_2	ZnO	70	55	82
9	$Pd(^tBu_3P)_2$	B_2pin_2	ZnO	70	<5	--
10	$Pd(^tBu_3P)_2$	B_2hex_2	ZnO	70	<5	--
11	$Pd(PPh_3)_4$	B_2cat_2	ZnO	70	36	83
12	$Pd(Amphos)_2$	B_2cat_2	ZnO	70	81	89
13	AdBrettPhos Pd G3	B_2cat_2	ZnO	70	44	87
14	SPhos Pd G3	B_2cat_2	ZnO	70	92	93
15	SPhos Pd G3	B_2cat_2	ZnO	25	78	87



Reaction conditions: **1a** (0.3 mmol, 1 equiv.), D_2O (4.0 equiv.), [Pd/L] (5 mol%), additive (2.0 equiv.), THF (0.2 M), N_2 atmosphere, T °C, 12 h. Yield and deuterated ratio of **2a** was determined by ^{19}F NMR with 2-fluorotoluene as an internal standard. DABCO, 1,4-diazabicyclo[2.2.2]octane.

aromatic compounds during phase one metabolism[54,55]. Our strategy offers a way to recover these drug metabolites, converting them back into metabolic hotspot-blocked compounds. For example, when the flurbiprofen metabolite[56] methyl ester was treated with triflic anhydride, the resulting aryl triflate served as a substrate for the deuteration reaction, leading to the conversion of the drug metabolite into a more metabolically stable compound, [^{2}H]-flurbiprofen methyl ester (**4k**). Overall, the approach showcases high reactivity in the presence of a variety of functional groups, making it a versatile method for incorporating deuterium into various drug molecules through late-stage modifications.

Preliminary mechanistic studies

Control experiments with 4-phenylphenyl triflate as substrate show that the deuteration reaction proceeds smoothly, yielding the deuteration product in 69% isolated yield with a 95% deuterated ratio in the presence of D_2O and B_2pin_2 (Fig. 4a). However, when only B_2pin_2 is used without D_2O, the reaction shows <5% conversion under standard conditions. The results are consistent with the mechanism in which the in-situ generated D^- equivalent from D_2O plays a key role in enabling efficient transmetallation with aryl palladium. Control experiments with aryl bromide and aryl chloride substrates show a similarly important role of D_2O for high conversion (Supplementary Information Pages S54–S55). When a typical deuteride donor D-Bpin was applied instead of diboron and D_2O, an efficient hydride transfer reaction occurred, producing **4a** in 41% isolated yield with a 70% deuterated ratio. The results are consistent with the facile transmetallation between Ar-[Pd]-OTf and deuteride donor under reaction conditions. The palladium-catalyzed umpolung reaction of water in the presence of diboron has been reported[45,57,58], and our control experiments are consistent with a mechanism in which the aryl palladium undergoes transmetallation with the in-situ generated deuteride donor.

Based on the preliminary mechanistic study results, we propose a catalytic cycle (Fig. 4b). First, palladium(0) undergoes oxidative addition with diboron to form an intermediate **A**. Subsequently, deuterated water could coordinate to the Lewis acidic boron atom in intermediate **A** to form an tetracoordinated boron species, which then eliminates $DO\text{-}B(OR)_2$ to furnish palladium deuteride species intermediate **B**. Intermediate **B** exists in equilibrium with the deuteride-boron species and palladium(0). Simultaneously, the palladium(0) can undergo oxidative addition with aryl halides, producing an Ar-[Pd]-X species **C**. In the presence of a halide scavenger such as zinc salts, a cationic Ar-[Pd]$^+$ species **D** is generated[46,47]. The cationic palladium **D** favors the transmetallation with the in-situ generated deuteride species, rather than diboron, leading to Ar-[Pd]-D intermediate **E**. Finally, a reductive elimination process of **E** produces the deuterated product and regenerates palladium(0).

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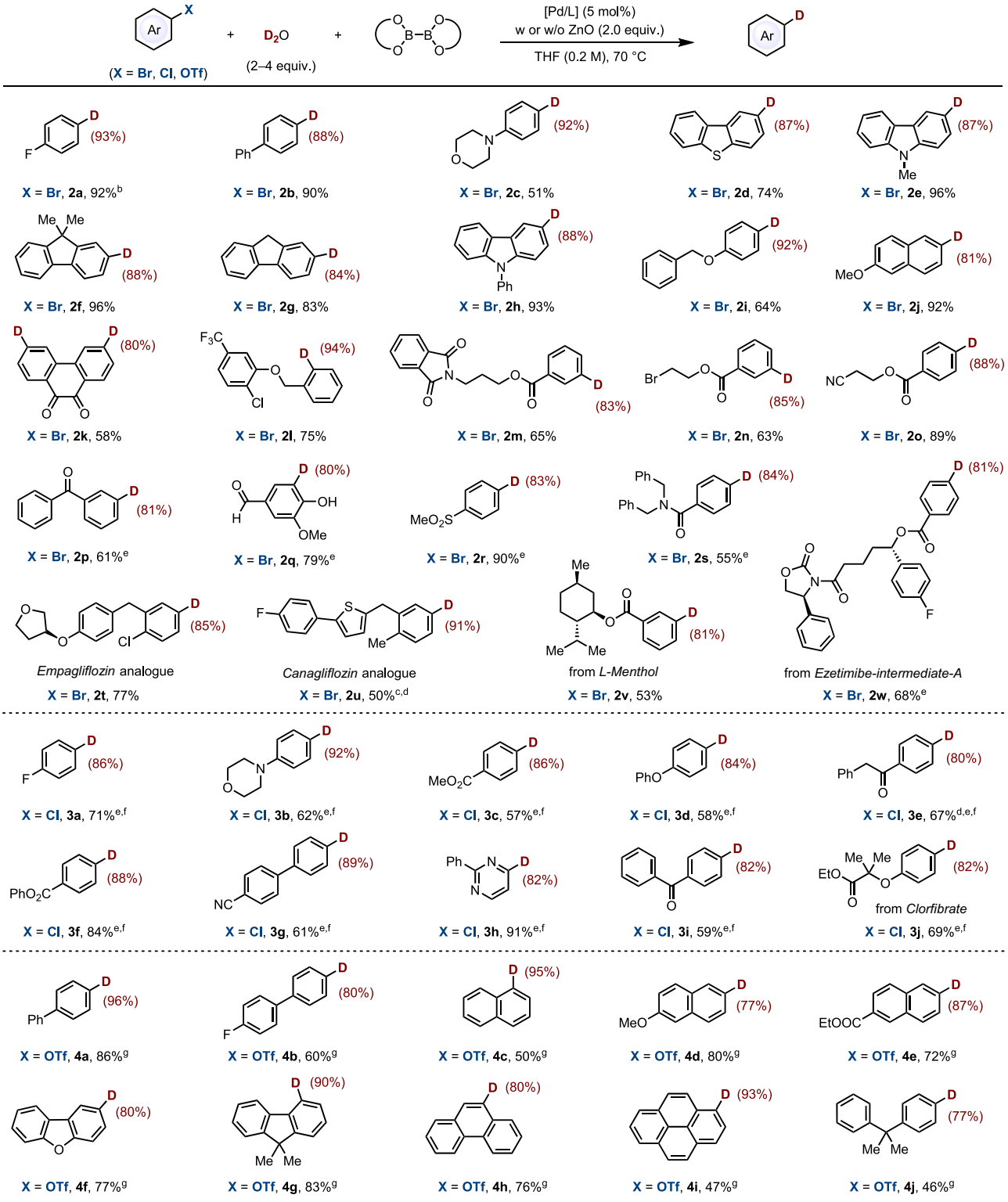

Fig. 2 | Substrate scope[a]. [a]Reaction conditions: aryl (pseudo)halide (0.3–0.9 mmol, 1 equiv.), SPhos Pd G3 (5 mol%), ZnO (2.0 equiv.), B_2cat_2 (2.0 equiv.), D_2O (2.0–4.0 equiv.), THF (0.2 M), N_2 atmosphere, 70 °C, 12 h, isolated yields are reported, and deuterated ratios are reported in parentheses. [b]Yield and deuterated ratio were determined by ^{19}F NMR. [c]ZnO and B_2cat_2 (4.0 equiv.).[d]D_2O (8.0 equiv.) [e]B_2eg_2 (2.0 equiv.). [f]AdBrettPhos Pd G3 (5–15 mol%). [g]Pd($^tBu_3P$)$_2$ (5–20 mol%), w/o ZnO, B_2hex_2 (2.0 equiv.).

Discussion

In conclusion, we have developed an efficient palladium-catalyzed deuteration reaction of aryl (pseudo)halides with D_2O as deuterium source. The reaction is enabled by the merger of a D_2O umpolung reaction with a cross-coupling reaction via a cationic aryl palladium intermediate. The efficient method for incorporating deuterium into drug molecules with D_2O makes it a practical approach for late-stage deuteration. Further investigation into the deuteration reactions of other electrophiles via the cationic palladium intermediates is in progress in our lab.

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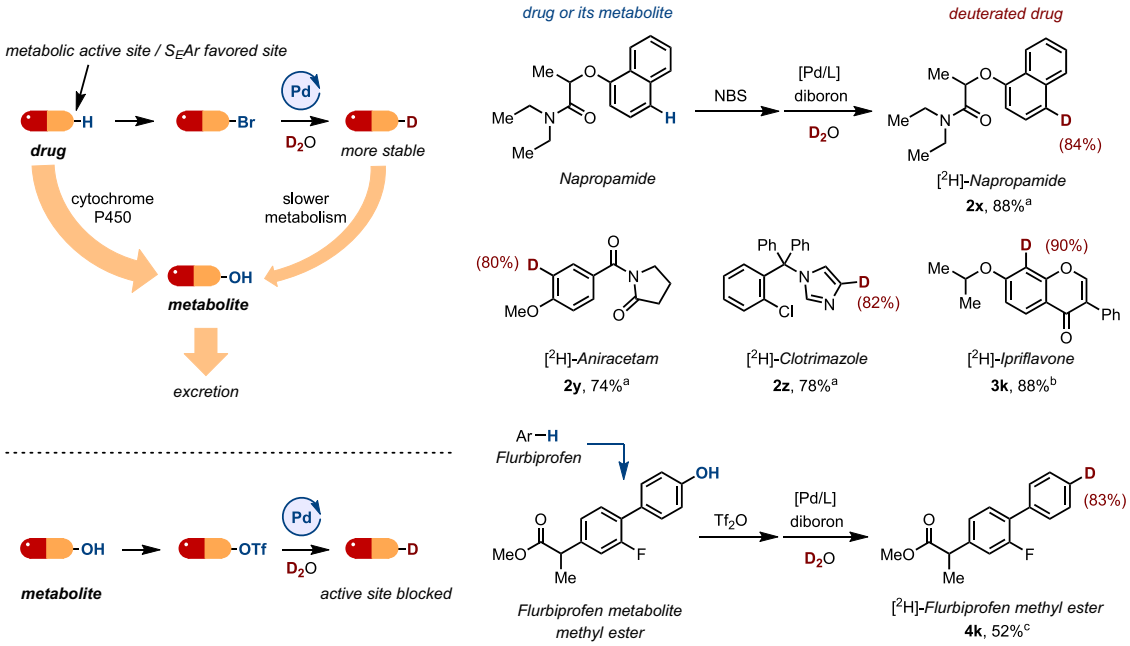

Fig. 3 | Modification and deuteration reaction of drug derivatives. [a]Reaction conditions: aryl (pseudo)halide (0.3 mmol, 1 equiv.), SPhos Pd G3 (5 mol%), ZnO (2.0 equiv.), B_2eg_2 (2.0 equiv.), D_2O (4.0 equiv.), THF (0.2 M), N_2 atmosphere, 70 °C, 12 h, isolated yields are reported, and deuterated ratios are reported in parentheses. [b]AdBrettPhos Pd G3 (5 mol%). [c]Pd(^{t}Bu$_3$P)$_2$ (5 mol%), w/o ZnO, B_2hex_2 (2.0 equiv.).

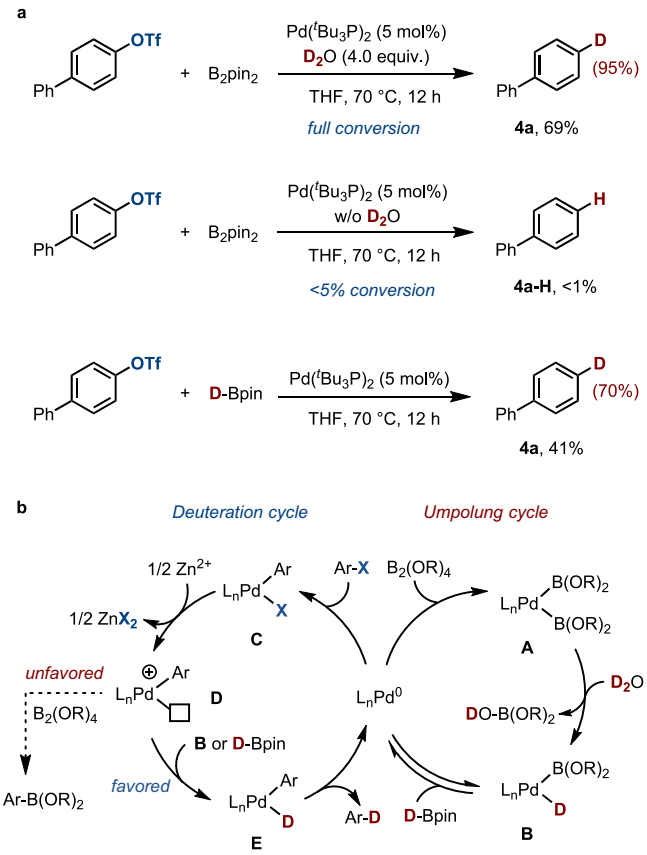

Fig. 4 | Preliminary mechanistic study. a Control experiment. **b** Plausible mechanism for the palladium-catalyzed deuteration reaction of aryl halides with deuterium oxide.

Methods

General procedure for deuteration reactions of aryl bromides

Under a nitrogen atmosphere, SPhos Pd G3 (11.7 mg, 15 μmol, 5.0 mol %), ZnO (48.6 mg, 0.600 mmol, 2.00 equiv.), B_2cat_2 (142.8 mg, 0.600 mmol, 2.00 equiv.), and aryl bromide (0.300 mmol, 1.00 equiv.) were added to a 4 mL vial containing a magnetic stir bar. Subsequently, D_2O (24.3 mg, 1.20 mmol, 4.00 equiv.) in THF (1.5 mL, $c = 0.2$ M) was added into the tube. Subsequently, the reaction mixture was stirred vigorously at 70 °C for 12 h in a heating block. After that, the reaction vessel was opened to air, and the resulting mixture was concentrated by rotary evaporation. The residue was purified by chromatography on silica gel to obtain the pure product.

General procedure for deuteration reactions of aryl chlorides

Under a nitrogen atmosphere, AdBrettPhos Pd G3 (15.2 mg, 15.0 μmol, 5.0 mol%), ZnO (48.6 mg, 0.600 mmol, 2.00 equiv.), B_2eg_2 (84.6 mg, 0.600 mmol, 2.00 equiv.), and aryl chloride (0.300 mmol, 1.00 equiv.) were added to a 4 mL vial containing a magnetic stir bar. Subsequently, D_2O (24.3 mg, 1.20 mmol, 4.00 equiv.) in THF (1.5 mL, $c = 0.2$ M) was added into the tube. Subsequently, the reaction mixture was stirred vigorously at 70 °C for 12 h in a heating block. After that, the reaction vessel was opened to air, and the resulting mixture was concentrated by rotary evaporation. The residue was purified by chromatography on silica gel to obtain the pure product.

General procedure for deuteration reactions of aryl triflates

Under a nitrogen atmosphere, Pd(^{t}Bu$_3$P)$_2$ (7.8 mg, 15 μmol, 5.0 mol%), B_2hex_2 (152.4 mg, 0.600 mmol, 2.00 equiv.), and aryl triflate (0.300 mmol, 1.00 equiv.) were added to a 4-mL vial containing a magnetic stir bar. Subsequently, D_2O (24.3 mg, 1.20 mmol, 4.00 equiv.) in THF (1.5 mL, $c = 0.2$ M) was added into the tube. Subsequently, the reaction mixture was stirred vigorously at 70 °C for 12 h in a heating block. After that, the reaction vessel was opened to air, and the resulting mixture was concentrated by rotary evaporation. The residue was purified by chromatography on silica gel to obtain the pure product.

Data availability

The data supporting the findings of this study are available within the article and its Supplementary Information file. All other data were available from the corresponding author upon request.

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Author contributions

L.Z. conceived the project. Y.C., R.Y. developed the deuteration reaction. R.Y., Y.C. explored the substrate scope. T.Z., Q.G. prepared the substrates. Y.C. investigated the mechanism with input from Y.Y. L.Z. wrote the manuscript with the input from all authors. L.Z. directed the project.

Competing interests

The authors declare no competing interests.

Additional information

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