nature portfolio

Peer Review File

Pd-catalyzed deuteration of aryl halides with deuterium oxide

Corresponding Author: Professor Li Zhang

This file contains all reviewer reports in order by version, followed by all author rebuttals in order by version.

Version 0:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
Incorporation of deuterium into molecules holds significant importance in various fields of chemistry. Numerous advances in this area have been achieved. This manuscript reports a Pd-catalyzed dehalogenative deuteration reaction for the synthesis of deuterated arenes. The catalytic system employs a Buchwald 3rd generation palladium complex as the precatalyst, enabling dehalogenation using D_2O and diboron as the reducing agents. The substrate scope is extensive, encompassing a wide range of aryl halides and drug-like molecules, achieving moderate to good deuterium incorporating content, mostly between 80–90%.

While the manuscript is well prepared, my primary concern is that this chemistry lacks novelty. Palladium-catalyzed reductive dehalogenation has been thoroughly explored in previous studies, and this work offers limited conceptual advancement. In terms of deuteration techniques, state-of-the-art deuteration methods including electrochemical deuteration and H/D exchange reactions are already well-established, providing more impactful alternatives in both fundamental research and practical applications.

Given these considerations, I am unable to recommend the publication of this manuscript, as it does not meet the standards of fundamental importance or practical innovation required for this journal.

Reviewer #2

(Remarks to the Author)
In this study, Yao, Zhang, and coworkers developed an efficient palladium-catalyzed deuteration reaction of aromatic (pseudo)halides using D2O as a deuterium source. This reaction was achieved through the integration of a catalytic umpolung reaction of D2O and a cross-coupling reaction mediated by a cationic aryl palladium intermediate. Deuterium labeling technology is recognized as a crucial tool for improving the pharmacokinetics and pharmacodynamics of drug molecules. Therefore, the development of late-stage deuteration methods is a significant challenge in the field of drug discovery. They successfully developed a deuteration reaction of aryl bromides, chlorides, and triflates with heavy water under palladium catalysis. Notably, many aromatic drug molecules are metabolized to their phenolic forms due to electrophilic hydroxylation catalyzed by cytochrome P450 enzymes (CYPs). As a demonstration, the authors prepared a triflylated substrate from an oxidative metabolite of pharmacologically active compound and performed deuteration. Although this approach is limited to substrates without other groups that can be triflylated, this strategy significantly demonstrates the utility of this method. I consider this manuscript contains original and important results and deserves publication in Nature Communications after revision of the following points:

1. Since D2O is the most critical reagent in this study, its more detailed information such as deuterium purity should be noted in the Supporting Information.

2. Results for optimization of reaction conditions using triflate substrate is not shown. Since transformation of triflates is significant point in this study, more details should be provided. In contrast, control experiments were only conducted using a triflate substrate. Control experiments using bromide or chloride substrate should be performed to discuss the similarity or difference between these substrates because conditions used are different.

3. Given that the reaction proceeded efficiently with HBpin, it is reasonable to hypothesize the formation of D-Bpin in the

reaction system. It is recommended to detected D-Bpin such as by 1H or 2H NMR or MS analysis. Conducting the reaction using D-Bpin (e.g. J. Am. Chem. Soc. 2022, 144, 18359–18374) is also recommended.

4. The authors optimized the reaction conditions using deuterated fluorobenzene 2a as the product of the deuteration reaction. However, despite the low boiling point of fluorobenzene (128 ºC), the yield was determined by 19F NMR rather than GC. More detailed procedures for this screening experiment should be provided including workup procedures and analytical method either in the manuscript or the Supporting Information.

5. There are several typos in the manuscript. Some of them are listed below. More careful preparation or third-party editing is strongly recommended.
· Line 27 and 29: "psuedo" should be "pseudo."
· Line 91: "hinderance" should be "hindrance."
· Line 104: "N-heterocyles" should be "N-heterocycles."
· Line 129: "iproflavon" should be "ipriflavone."
· Line 144: "paratheses" should be "parentheses."

6. In the catalytic cycle of the proposed reaction mechanism (Fig. 5b), Zn2+ and ZnX2 should be revised to 1/2Zn2+ and 1/2ZnX2, respectively. Also replace "D– equiv." with "D-Bpin."

7. In the SI, for high-resolution mass spectrometry (HRMS) where the compound contains atoms with isotopes of significant abundance (e.g. Cl, Br), the measured isotope should be quoted.

Reviewer #3

(Remarks to the Author)
Zhang et. al developed an efficient palladium catalyzed deuteration reaction of aryl(pseudo)halides with D2O as deuterium source. The manuscript is well written, properly explained. I recommend the manuscript for publication in your journal provided they address the following points:
a) In Figure 3, the compounds bearing electron withdrwaing groups such as aldehyde, acids etc are missing. The experiments with electron withdrawing groups must be performed.
b) In Figure 5, the formation of intermediate B from intermediate A should be explained.
c) In supporting information, most of the compounds contain water, NMR solvent, grease peak in high amount. Please remove those peak as much as possible.

Version 1:

Reviewer comments:

Reviewer #2

(Remarks to the Author)
The authors have adequately addressed all my comments and provided the necessary revisions, including additional experimental data, clarifications in the manuscript and Supporting Information, and corrections to typographical errors. The newly included control experiments and mechanistic discussions strengthen the validity of their findings. Given these improvements, I find the manuscript suitable for publication in Nature Communications in its current form.

Reviewer #3

(Remarks to the Author)
The author address all the point raised by the reviewers and included in the manuscript. I recommend the paper for publication.

Reviewer #1 Comments

Reviewer #1 Comment 1:

Incorporation of deuterium into molecules holds significant importance in various fields of chemistry. Numerous advances in this area have been achieved. This manuscript reports a Pd-catalyzed dehalogenative deuteration reaction for the synthesis of deuterated arenes. The catalytic system employs a Buchwald 3rd generation palladium complex as the precatalyst, enabling dehalogenation using D_2O and diboron as the reducing agents. The substrate scope is extensive, encompassing a wide range of aryl halides and drug-like molecules, achieving moderate to good deuterium incorporating content, mostly between 80–90%.

Our Response:

We thank the referee for the appraisals.

Reviewer #1 Comment 2:

While the manuscript is well prepared, my primary concern is that this chemistry lacks novelty. Palladium-catalyzed reductive dehalogenation has been thoroughly explored in previous studies, and this work offers limited conceptual advancement. In terms of deuteration techniques, state-of-the-art deuteration methods including electrochemical deuteration and H/D exchange reactions are already well-established, providing more impactful alternatives in both fundamental research and practical applications.

Given these considerations, I am unable to recommend the publication of this manuscript, as it does not meet the standards of fundamental importance or practical innovation required for this journal.

Our Response:

1. Palladium-catalyzed deuteration of aryl (pseudo)halide with deuteride sources has been reported (e.g. *Nature* **2021**, *600*, 444). However, expensive deuteride sources, such as D_2 (230€/mol) or $NaBD_4$ (1240€/mol), are required for the reactions. The deuteration of aryl (pseudo)halides using the most cost-effective deuterium source, D_2O (15€/mol), is a highly desirable transformation but has not been accomplished with palladium catalysis, primarily due to the lack of an umpolung strategy. In our study, we successfully applied D_2O for the palladium-catalyzed deuteration of aryl halides based on a catalytic umpolung cycle. Our strategy for achieving this highly desirable transformation with D_2O differentiates itself from previous palladium-catalyzed reductive dehalogenation processes with deuteride sources.
2. We agree that electrochemical deuteration is an important advance in this area, and a variety of aryl halides could be deuterated with high reactivity (*CCS Chem.* **2021**, *3*, 2669). However, it should be noted that few late-stage deuteration examples are presented in the electrochemical method. The palladium-catalyzed strategy offers advantages for late-stage

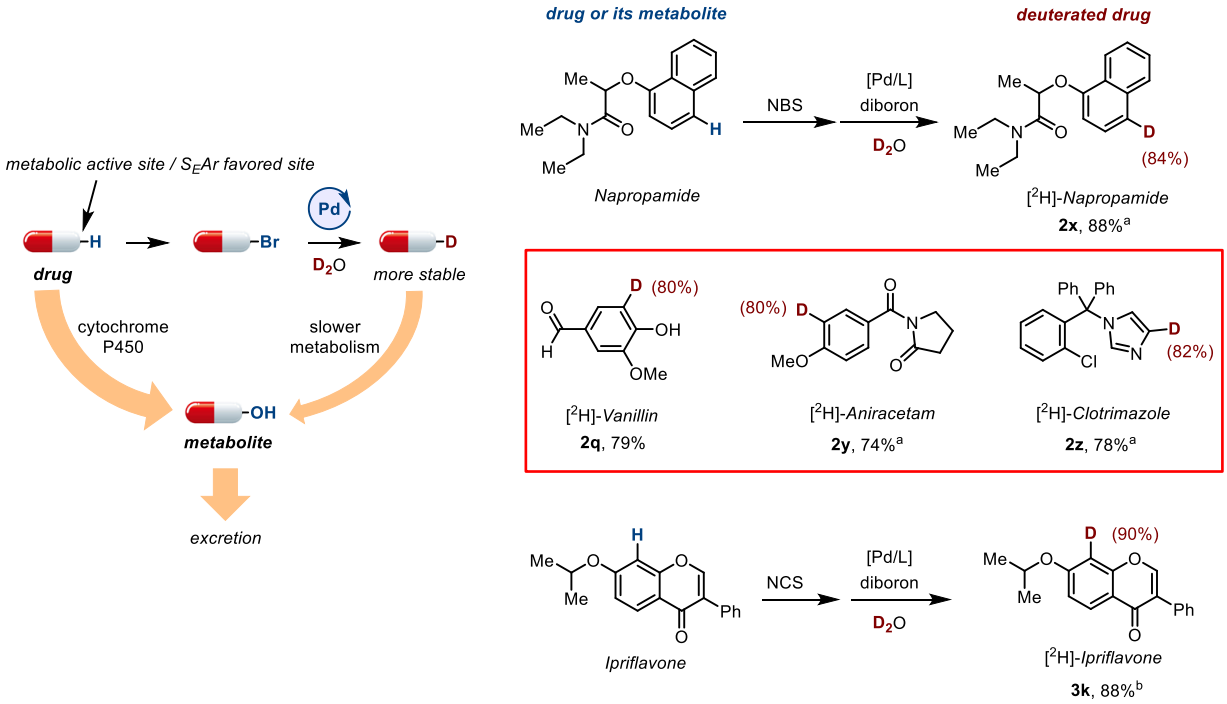
deuteration, due to the selective oxidative addition of Pd(0) to C-halogen bonds in the presence of a variety of functional groups. To further demonstrate this point, we have added additional late-stage deuteration examples of drug compounds **2q, 2y, 2z** to the revised manuscript in Figs. 3, 4.

3. H/D exchange with D_2O is widely regarded as a valuable transformation (*Angew. Chem. Int. Ed.* **2024**, *63*, e202404421). However, deuteration with H/D exchange strategy is typically non-selective. Our S_EAr/deuteration protocol (see below) facilitates the selective conversion of C–H bonds to C–D bonds using D_2O as the deuterium source. To further demonstrate this point, we have added additional selective deuteration examples of drug compounds to the revised manuscript in Figs. 3, 4.

We believe the umpolung cycle for *in situ* generation of deuteride, which enables the deuteration of aryl halides with D_2O, combined with the practical approach for selective late-stage deuteration of drug molecules, may provide a fundamentally different strategy to address the long-standing challenge of late-stage deuteration. We hope the reviewer could agree with us based on the additional results and explanations provided.

Changes/Additions to the revised manuscript:

Pages 5–6, additional examples of late-stage deuteration have been added:



Reviewer #2 Comments

Reviewer #2 Comment 1:

In this study, Yao, Zhang, and coworkers developed an efficient palladium-catalyzed deuteration reaction of aromatic (pseudo)halides using D2O as a deuterium source. This reaction was achieved through the integration of a catalytic umpolung reaction of D2O and a cross-coupling reaction mediated by a cationic aryl palladium intermediate. Deuterium labeling technology is recognized as a crucial tool for improving the pharmacokinetics and pharmacodynamics of drug molecules. Therefore, the development of late-stage deuteration methods is a significant challenge in the field of drug discovery. They successfully developed a deuteration reaction of aryl bromides, chlorides, and triflates with heavy water under palladium catalysis. Notably, many aromatic drug molecules are metabolized to their phenolic forms due to electrophilic hydroxylation catalyzed by cytochrome P450 enzymes (CYPs). As a demonstration, the authors prepared a triflylated substrate from an oxidative metabolite of pharmacologically active compound and performed deuteration. Although this approach is limited to substrates without other groups that can be triflylated, this strategy significantly demonstrates the utility of this method.

Our Response:

We thank the referee for the appraisals.

Reviewer #2 Comment 2:

I consider this manuscript contains original and important results and deserves publication in Nature Communications after revision of the following points:

1. Since D2O is the most critical reagent in this study, its more detailed information such as deuterium purity should be noted in the Supporting Information.

Our Response:

We thank the reviewer for pointing out the clarification on the purity of D_2O. A note has been added to the revised Supporting Information on Page S8.

Changes/Additions to the revised Supporting Information:

Page S8, bottom, a note for the purity of D_2O has been added, it reads as follow:

Note: The commercial deuterated oxide (D_2O) for the deuteration reaction had a deuteration ratio of 99.9%.

Reviewer #2 Comment 3:

2. Results for optimization of reaction conditions using triflate substrate is not shown. Since transformation of triflates is significant point in this study, more details should be provided. In contrast, control experiments were only conducted using a triflate substrate. Control experiments using bromide or chloride substrate

should be performed to discuss the similarity or difference between these substrates because conditions used are different.

Our Response:

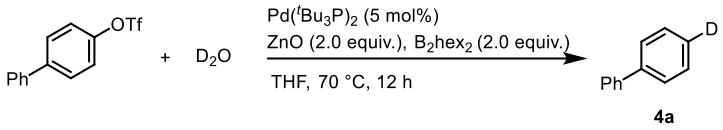
(1) The results for the optimization of reaction conditions for Ar-OTf substrate have been added to the revised Supporting Information in Table S2 on page S13.

(2) Control experiments with Ar-Br and Ar-Cl substrates have been carried out. 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 cationic aryl palladium. The control experiment results have been added to the revise Supporting Information on pages S54–55.

(3) The reaction conditions for Ar-Br, Ar-Cl, and Ar-OTf vary with respect to the palladium catalysts and halide scavenger. More electron-rich and hindered catalysts are required for inert Ar-Cl substrates, while a halide scavenger is not necessary for Ar-OTf substrates. The additional discussion has been added to the revised manuscript on page 4.

Changes/Additions to the revised Supporting Information:

Page S13, the optimization of reaction conditions using triflate substrate has been added. It reads as follow:

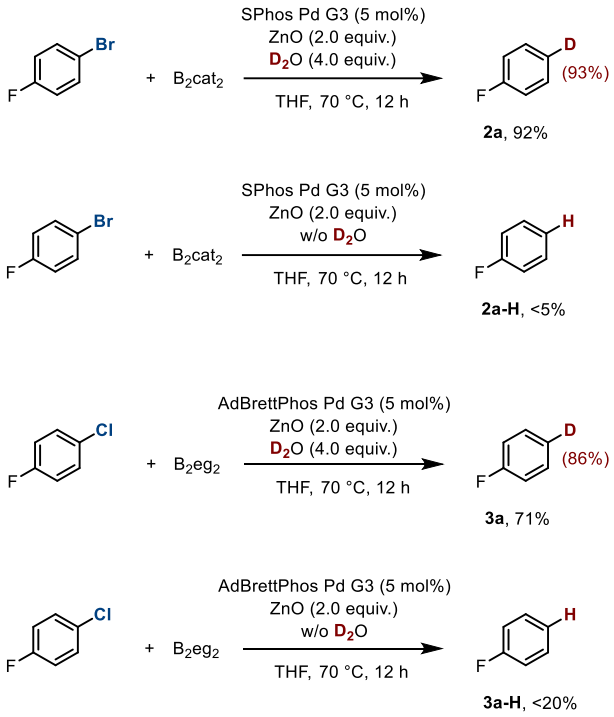


4a

Entry	Change of reaction conditions	Yield (deuterated ratio)[c]
1	None	86% (96%)
2[b]	Change B_2hex_2 to B_2pin_2	86% (94%)
3[b]	Change B_2hex_2 to B_2cat_2	<20%
4[b]	Change B_2hex_2 to B_2nep_2	62% (90%)
5[b]	Change B_2hex_2 to $B_2(OH)_4$	56% (43%)
6[b]	Change B_2hex_2 to $B_2(NMe_2)_4$	<5%
7	Change $Pd(^tBu_3P)_2$ to SPhos Pd G3	<5%
8	Change $Pd(^tBu_3P)_2$ to $Pd(OAc)_2$ (5 mol%) + dppf (10 mol%)	<5%
9	Change $Pd(^tBu_3P)_2$ to $Pd(OAc)_2$ (5 mol%) + AntPhos (10 mol%)	<5%
10	Change $Pd(^tBu_3P)_2$ to $Pd(OAc)_2$ (5 mol%) + $P(MeOPh)_3$ (10 mol%)	<5%

[a] Aryl triflate (0.3 mmol), D_2O (4.0 equiv.), $Pd(^tBu_3P)_2$ (5 mol%), B_2hex_2 (2.0 equiv.), THF (0.2 M), 70 °C, 12 h. [b] D_2O (8.0 equiv.), [c] Yield of isolated product, deuterated ratio was determined by the integration of ^1H NMR.

Pages S54–55, the control experiments with Ar-Br and Ar-Cl have been added. It reads as follow:



Changes/Additions to the revised manuscript:

Page 4, the discussion on the difference between different aryl (pseudo)halide has been revised. It reads as follow:

"The oxidative addition of palladium(0) to aryl triflate leads to Ar-[Pd]-OTf, which does not involve coordinative halide species, eliminating the need for a halide scavenger such as ZnO (see Supporting Information for details)."

Page 4, the discussion on the control experiment results has been revised. It reads as follow:

"Control experiments with aryl bromide and aryl chloride substrates show similarly important role of D_2O for high conversion (see Supporting Information for details)."

Reviewer #2 Comment 4:

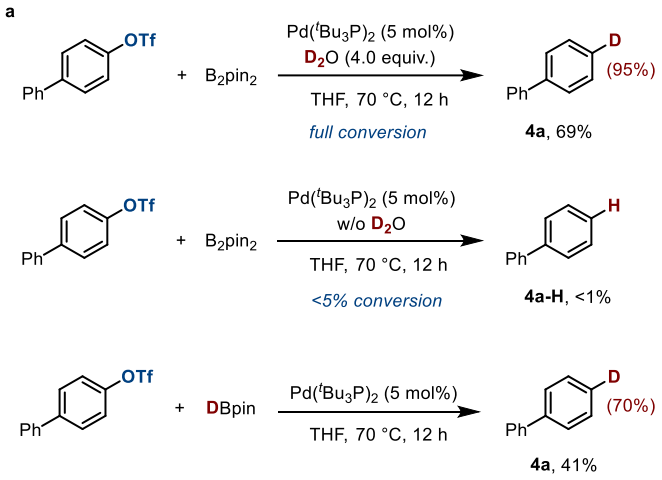
3. Given that the reaction proceeded efficiently with HBpin, it is reasonable to hypothesize the formation of D-Bpin in the reaction system. It is recommended to detected D-Bpin such as by 1H or 2H NMR or MS analysis. Conducting the reaction using D-Bpin (e.g. J. Am. Chem. Soc. 2022, 144, 18359–18374) is also recommended.

Our Response:

An additional control experiment with D-Bpin has been included, yielding the deuterated product in 41% yield with a 70% deuteration ratio. The results are consistent with the umpolung of D_2O to form a deuteride source under reaction conditions. We have also tried to detect the D-Bpin under reaction conditions, and the HRMS spectrum results are consistent with the formation of D-Bpin in the reaction mixture. The additional control experiments are summarized in the revised manuscript in Fig. 5a, with full details provided in the revised Supporting Information on pages S50–S53.

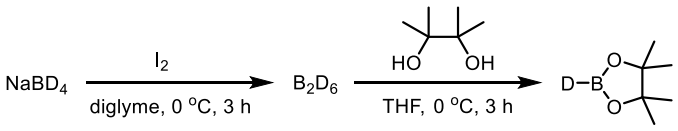
Changes/Additions to the revised manuscript:

Page 7, Fig. 5a, the control experiment with D-Bpin has been added. It reads as follow:

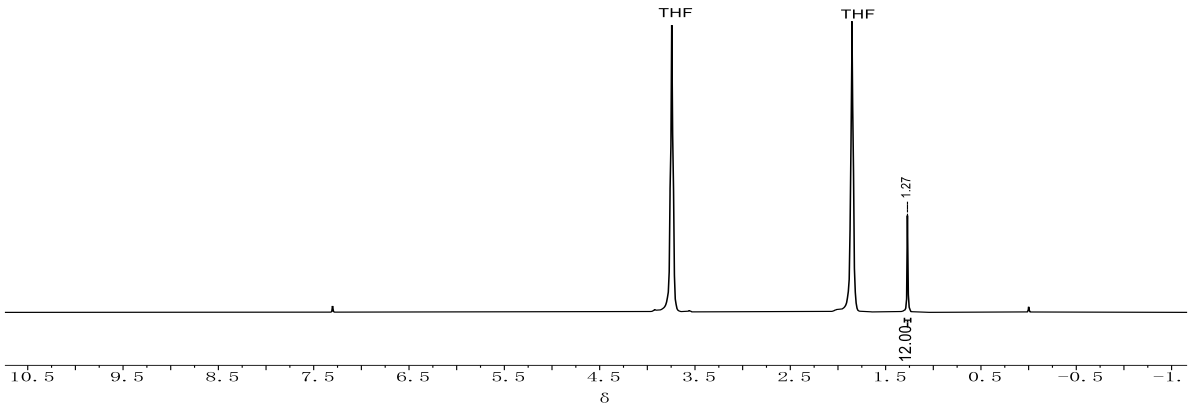


Changes/Additions to the revised Supporting Information:

Pages S50–53, the procedure for the preparation of D-Bpin has been added. It reads as follow:



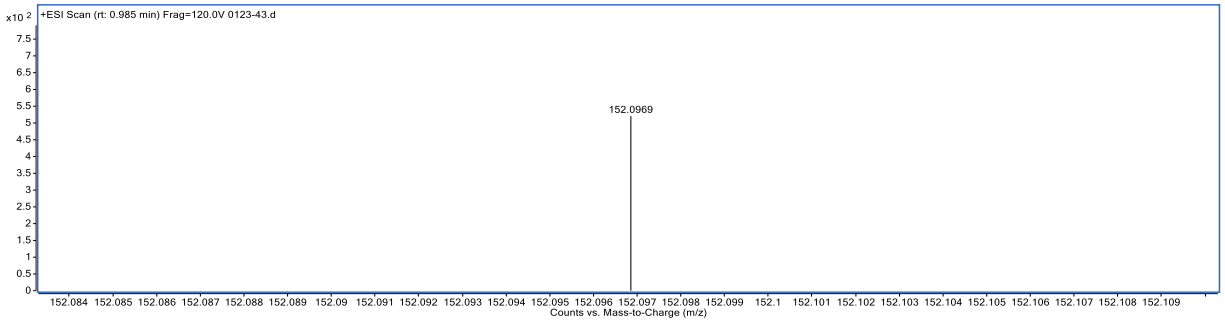
^{1}H NMR spectrum of D-Bpin



Page S54, the HRMS analysis of the reaction mixture has been added. It reads as follow:

Under a nitrogen atmosphere, Pd(^{t}Bu$_3$P)$_2$ (7.8 mg, 15 μmol, 5 mol%), B_2pin_2 (152.4 mg, 0.600 mmol, 2.00 equiv.), and 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 for 12 h at room temperature. After that, the resulting mixture was diluted with MeCN. HRMS analysis of the mixture shows the formation of D-Bpin.

HRMS ESI (m/z) calc'd for $C_6H_{12}D^{11}BO_2Na^+$ [M+Na]$^+$, 152.0964; found, 152.0969. Deviation: +3.2 ppm.



Reviewer #2 Comment 5:

4. The authors optimized the reaction conditions using deuterated fluorobenzene 2a as the product of the deuteration reaction. However, despite the low boiling point of fluorobenzene (128 ºC), the yield was

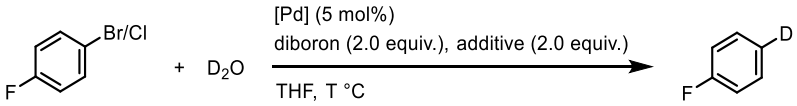
determined by 19F NMR rather than GC. More detailed procedures for this screening experiment should be provided including workup procedures and analytical method either in the manuscript or the Supporting Information.

Our Response:

A general procedure, including the workup steps and analytical methods for the optimization of the reaction conditions, has been added to the revised Supporting Information on page S9. The ^{19}F NMR was chosen for analysis because it allows determination of both yield and deuterated ratio in a single spectrum, making it more convenient for deuterated ratio analysis. A representative ^{19}F NMR of the reaction mixture has also been include in the revised Supporting Information on page S12.

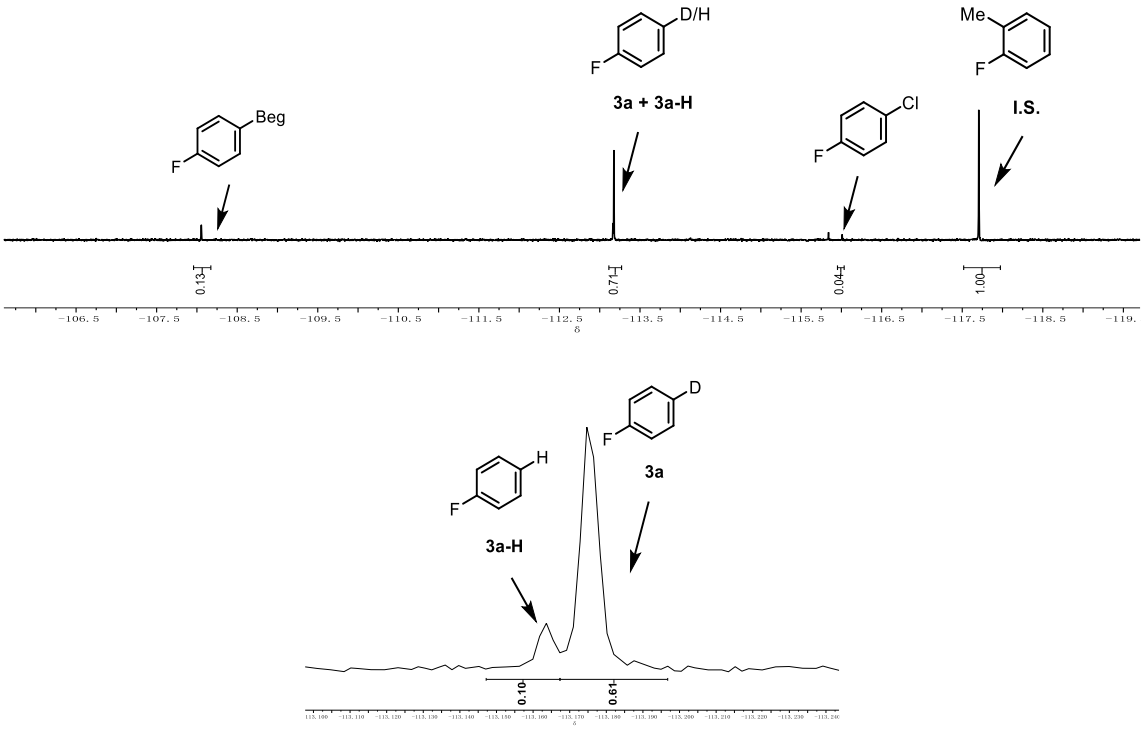
Changes/Additions to the revised Supporting Information:

Page S9, a general procedure for reaction condition optimization of aryl halide substrates has been added. It reads as follow:



Under a nitrogen atmosphere, palladium catalyst (5.0 mol%), additive (2.00 equiv.), diboron (2.00 equiv.), and aryl halide (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 T °C for indicated time in a heating block. After that, the reaction vessel was opened to air, and 2-fluorotoluene (33 μL, 0.30 mmol, 1.0 equiv.) was added as an internal standard and stirred for 3 min. After that, an aliquot of the organic phase was taken and diluted with $CDCl_3$ (0.5 mL). The yield and deuterated ratio were determined by ^{19}F NMR integration relative to the internal standard (standard: δ –117.7 ppm, fluorobenzene: δ –113.16 ppm, 4-[^{2}H]-fluorobenzene: δ –113.18 ppm).

Page S12, detailed analytical methods used for the screening experiments have been added. It reads as follow:



Deuterium incorporation: 86% ^{2}H/molecule (D ratio = 0.61 / 0.71 * 100% from ^{19}F NMR integration)

Reviewer #2 Comment 6:

5. There are several typos in the manuscript. Some of them are listed below. More careful preparation or third-party editing is strongly recommended.

· Line 27 and 29: "psuedo" should be "pseudo."

· Line 91: "hinderance" should be "hindrance."

· Line 104: "N-heterocyles" should be "N-heterocycles."

· Line 129: "iproflavon" should be "ipriflavone."

· Line 144: "paratheses" should be "parentheses."

Our Response:

We thank the reviewer for pointing out these typos. We have thoroughly reviewed the manuscript and ensured that there are no additional spelling errors.

Reviewer #2 Comment 7:

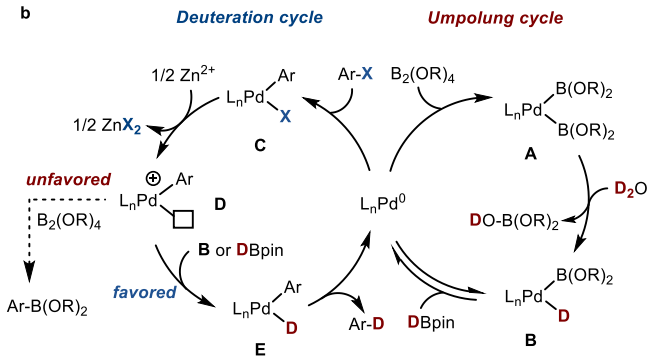
6. In the catalytic cycle of the proposed reaction mechanism (Fig. 5b), Zn2+ and ZnX2 should be revised to 1/2Zn2+ and 1/2ZnX2, respectively. Also replace "D– equiv." with "D-Bpin."

Our Response:

We have revised the Zn^{2+} and ZnX_2 to 1/2 Zn^{2+} and 1/2 ZnX_2, and replaced the D^- equiv. with D-Bpin in the revised manuscript in Fig 5b.

Changes/Additions to the revised manuscript:

Page 7, Fig. 5b, the plausible catalytic cycle has been revised. It reads as follow:



Reviewer #2 Comment 8:

7. In the SI, for high-resolution mass spectrometry (HRMS) where the compound contains atoms with isotopes of significant abundance (e.g. Cl, Br), the measured isotope should be quoted.

Our Response:

In addition to the deuterium atom in the deuterated products, compounds containing Cl or Br (**2l**, **2n**, **2t**, **2z**, **2m-S**, **2n-S**, **2o-S**, **3k-S**) have been labeled with isotopes ^{35}Cl and ^{79}Br for HRMS analysis results, in the revised Supporting Information.

Reviewer #3 Comments

Reviewer #3 Comment 1:

Zhang et. al developed an efficient palladium catalyzed deuteration reaction of aryl(pseudo)halides with D2O as deuterium source. The manuscript is well written, properly explained.

Our Response:

We thank the referee for the appraisals.

Reviewer #3 Comment 2:

I recommend the manuscript for publication in your journal provided they address the following points:

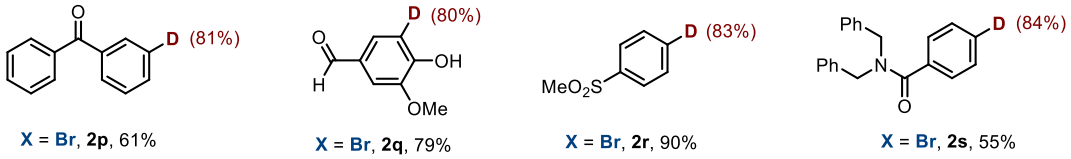
a) In Figure 3, the compounds bearing electron withdrwaing groups such as aldehyde, acids etc are missing. The experiments with electron withdrawing groups must be performed.

Our Response:

We have added four additional substrates with electron withdrawing groups (**2p-2s**), including ketone, aldehyde, sulfone, and amide, to the revised manuscript in Figure 3 on page 6. The deuteration reactions also work well for these additional substrates bearing electron withdrawing groups.

Changes/Additions to the revised manuscript:

Page 6, Fig. 3, additional substrates with electron-withdrawing groups have been added, it reads as follow:



Reviewer #3 Comment 3:

b) In Figure 5, the formation of intermediate B from intermediate A should be explained.

Our Response:

We thank the reviewer for pointing out the unclarity in the transformation from intermediate **A** to intermediate **B**. To improve clarity, we have added the side product of this step, DO-B(OR)$_2$, to the catalytic cycle in the revised manuscript. Deuterated water can coordinate to the Lewis acidic boron center of intermediate **A** to form a tetracoordinated boron species, which then eliminates DO-B(OR)$_2$ to furnish palladium deuteride species. A similar elimination process has been

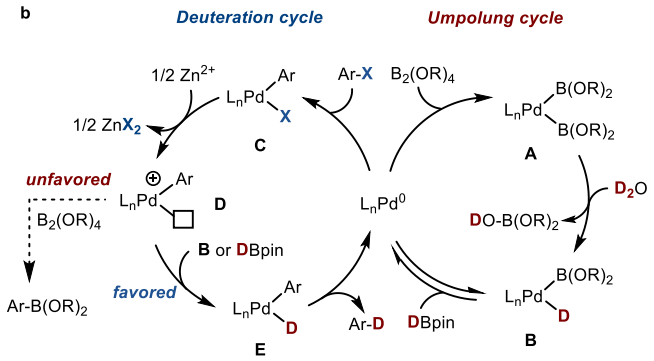
reported (*J. Am. Chem. Soc.* **2016**, *138*, 6107) and is cited as ref. 57 in the revised manuscript. The discussion of this step has also been added to the revised manuscript on page 7.

Changes/Additions to the revised manuscript:

*Page 7, middle, the discussion on the formation of Intermediate **B** has been revised. It reads as follow:*

"Subsequently, deuterated water could coordinate to the Lewis acidic boron atom in intermediate **A** to form a tetracoordinated boron species, which then eliminates DO-B(OR)$_2$ to furnish palladium deuteride species intermediate **B**."

Page 7, Fig. 5b, the plausible catalytic cycle has been revised. It reads as follow:



Reviewer #3 Comment 4:

c) In supporting information, most of the compounds contain water, NMR solvent, grease peak in high amount. Please remove those peak as much as possible.

Our Response:

We thank the reviewer for pointing out the water and grease peaks in NMR spectra. We have further purified the compounds to remove the grease peaks, and used higher-quality deuterated solvents for ^{1}H NMR measurements of compounds **2b, 2c, 2d, 2f, 2g, 2i, 2j, 2k, 2m, 3g, 4a, 4f**.