# Homogenous Palladium-Catalyzed Dehalogenative Deuteration and Tritiation of Aryl Halides with $D_2/T_2$ Gas

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**ABSTRACT:** Catalytic dehalogenative deuteration and tritiation with $D_2/T_2$ gas is a widely employed method for precisely introducing hydrogen isotopes into specific positions within organic molecules. While palladium(0) based heterogeneous catalysts, such as Pd/C, are commonly used for this purpose, challenges related to functional group tolerance and incomplete isotope incorporation are often encountered, particularly with respect to aryl bromides and chlorides. These long-standing issues pose a hurdle to achieving optimal results in tracer synthesis. The limited incorporation of isotopes for aryl bromides and chlorides presents a significant obstacle to the application of this method in the preparation of high specific activity tritium tracers. Herein, we present a novel palladium catalytic system using $Zn(OAc)_2$ as an additive, which enables homogeneous dehalogenative deuteration and tritiation using $D_2/T_2$ gas. Under mild reaction conditions, a wide range of drug-like aryl halides and pseudohalides undergo selective deuteration with complete isotope incorporation. The reaction displays excellent compatibility with diverse functional groups, including multiple bonds, *O*/*N*-benzyl, and cyano groups, which are frequently problematic in Pd/C reactions. Furthermore, this method was successfully applied to the tritiation of four halogenated pharmaceutically relevant molecules, resulting in predictable high specific activity per halogen atom (26.5-27.7 Ci/mmol). Notably, the developed system allows gram-scale preparation of a deuterium-containing intermediate, a crucial step in synthesizing a deuterium-labeled drug molecule. A reaction pathway involving a key intermediate, Pd(Ar)OAc, was proposed to activate hydrogen gas during dehalogenative deuteration and tritiation. This innovative method has potential to change the practice of dehalogenative deuteration and tritiation in the realm of hydrogen isotope labeling.

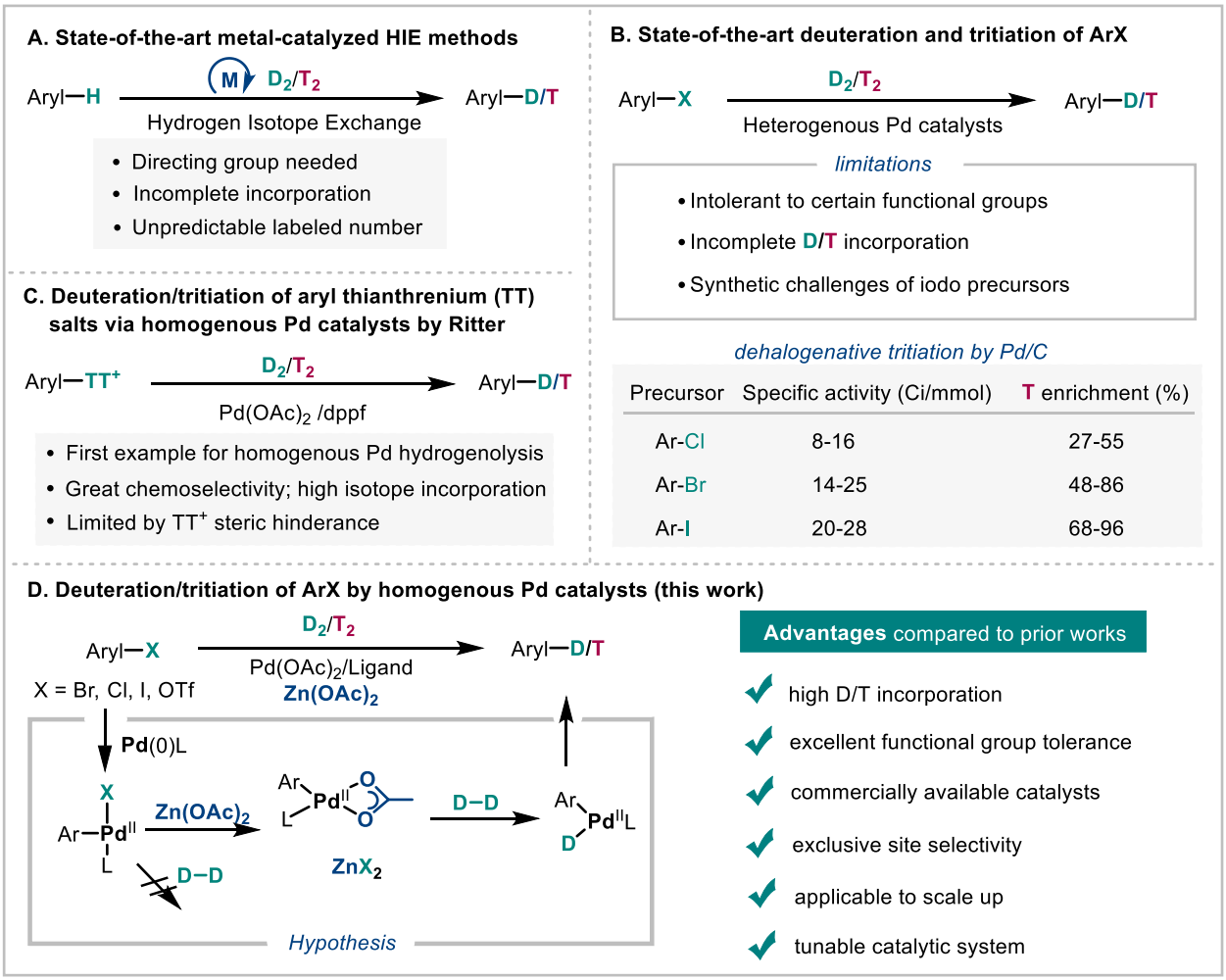
Hydrogen isotopically labeled compounds have found extensive utility across various domains, particularly in drug discovery and development in the pharmaceutical industry.[1-5] One significant application is their use as deuterium-labeled internal standards or tritium-labeled radiotracers. These isotopic labels enable accurate qualification and precise quantification of drug molecules and metabolites in both preclinical and clinical studies.[3-5] They provide distinct mass spectrum signals or highly sensitive radio signals that facilitate effective analysis while effecting minimal alternations to the chemical structure and physical properties of the molecules being studied. Moreover, deuterated compounds hold promise as potential novel drug candidates. Selectively incorporating deuterium into specific metabolic "soft spots" of a drug molecule may enhance its pharmacokinetic and toxicity profiles compared to its protio-containing counterparts. [6-7] This targeted deuterium labeling strategy presents an opportunity to optimize drug properties and improve therapeutic outcomes.

There are two primary approaches for synthesizing hydrogen isotopically labeled compounds: 1) hydrogen isotope exchange (HIE) and 2) reductive deuteration or tritiation. HIE is particularly attractive as it allows rapid and direct isotope incorporation at a late-stage to active pharmaceutical ingredients (API). Previously reported HIE methods typically employ metal catalysts such as iridium[8-11], nickel[12-13], iron[14], organic photocatalysts[15-16], and metal nanoparticles[17-18]. However, the majority of HIE methods require the use of directing groups, which consequently limits their substrate scopes (**Scheme 1A**). Substrates without a proper directing group often give low to no isotope incorporation. Furthermore, HIE often leads to multiple-site labeling, which can pose challenges in metabolism studies due to the potential loss of isotope labels during *in vitro* and *in vivo* studies. In many instances, HIE leads to incomplete isotope incorporation per carbon. Consequently, its utility is primarily limited to the preparation of tritium tracers, thus hindering its implementation in the synthesis of deuterium-labeled drug molecules that require precise and complete isotope incorporation. Additionally, a significant drawback of HIE tritiations is the lack of predictability in the total number of tritium atoms incorporated, namely the specific activity (SA) of the labeled products. In contrast, reductive deuteration or tritiation offers exclusive site selectivity due to the pre-defined location of unsaturated bonds or halogen atoms in the unlabeled precursors. While installing these pre-functional groups may require *de novo* synthesis, late-stage functionalization (LSF) towards aryl halides has been well-developed to make these precursors more readily accessible.[19-22] Multi-halogenated precursors can be utilized for the syntheses of high SA radiotracers. Therefore, dehalogenative tritiation of the corresponding aryl halides has become one of the most commonly employed methods for the preparation of tritium-labeled compounds.[23] It has also been successfully applied in the synthesis of deuterium-labeled drug candidates, including several clinically investigated compounds such as VX-984[24], d1-JNJ38877605[25], and VV116[26].

Dehalogenative deuteration or tritiation of aryl halides typically utilizes a heterogenous palladium catalyst (Pd/C) along with deuterium and tritium gas (**Scheme 1B**). This method has been employed for over half of a century, showcasing its

extensive range of applications.[27-28] However, despite its wide utility, this method has been afflicted by two enduring limitations. Firstly, the heterogenous catalytic system may not be able to selectively dehalogenate aryl halides in the presence of certain reducible functional groups (e.g., alkene, alkyne, N/O-benzyl, cyano, and nitro groups), significantly restricting its substrate scope. Moreover, it is widely recognized that use of aryl chlorides and aryl bromides as substrates typically result in partial D/T incorporation. This significantly hampers its potential for generating high SA tritium tracers. The root cause of this issue is unclear, although it has been proposed that the water content from Pd/C catalysts may contribute to partial D incorporation.[29] Furthermore, a trend of decreasing specific activity in the tritiated product is observed in the order of ArI > ArBr > ArCl, possibly due to the stronger affinity of aryl iodides with the Pd/C catalyst surface and their ability to exclude more water from catalytic sites compared to aryl bromides and chlorides. [23, 30-31] As a result, the preparation of multi-iodo arene precursors is often required when high SA tritium-labeled tracers are needed. However, this frequently introduces additional synthetical challenges compared to their bromo- and chloro-counterparts. Methods such as intensive drying of catalysts or the use of additives have been investigated as potential solutions to mitigate hydrogen isotope scrambling. However only limited improvements were shown in terms of deuterium incorporation.[29, 32] In contrast to heterogenous catalytic systems in dehalogenation with $D_2/T_2$ gas, significant progress has been made in dehalogenative deuteration using $D_2O$ or deuterated potassium formate via photo-[33], chemo-[34], and electrocatalysis[35] in recent years. While these advancements have expanded the scope of dehalogenative deuteration, transferring these methods to tritiations poses challenges due to the instability of high SA $T_2O$.[14, 36 37] Compared with $T_2O$, $T_2$ gas is preferred for tritium labeling due to its availability in high isotopic purity, stability, cost-effectiveness and practicality in terms of safe and precise handling with well-established commercially available manifolds. Therefore, the development of an effective and chemoselective dehalogenative deuteration and tritiation of aryl halides especially with aryl bromides and chlorides using $D_2/T_2$ gas as the isotope source is highly desirable.

**Scheme 1. Hydrogen isotope labeling methods**

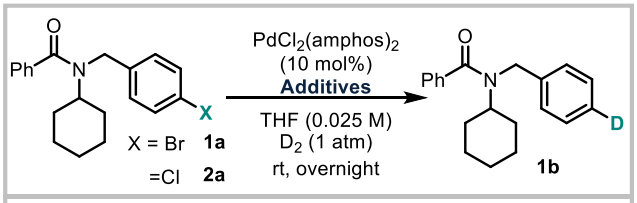



We envisioned that a homogeneous palladium system would possess the potential to address these issues. The critical challenge was that Pd was incapable of simultaneously activating dihydrogen molecules and Ar–X bonds.[38] Ritter and co-workers reported a seminal deuteration and tritiation of aryl thianthrenium ($TT^+$) salts using $D_2/T_2$ gas with homogenous Pd catalysts. This pioneering approach significantly enhances Pd reactivity toward $D_2/T_2$ via the formation of cationic Pd intermediate (**Scheme 1C**).[39] While this method is highly advantageous, it is constrained by the bulky nature of the thianthrenium group and its low atom economy especially when preparing deuterium drugs. This leads to the high sensitivity of

adjacent steric hindrance and poses the difficulty of multiple D/T installations. Moreover, these conditions lack reactivity for aryl halides.

We demonstrate below a mild homogenous Pd-catalyzed dehalogenative deuteration and tritiation with $D_2/T_2$ gas (**Scheme 1D**). This method exhibits remarkable compatibility with various functional groups, including multiple bonds, *O*/*N*-benzyl, and cyano groups. These functional groups are typically not tolerated under traditional HIE or Pd/C dehalogenation conditions. This method provides a quantitative level of D incorporations and high yields for drug-like aryl halides and pseudohalides. Moreover, this method affords tritium-labeled pharmaceutically relevant molecules with predictable high SA. Mechanistic studies suggest that dihydrogen splitting does not occur via Pd cation but instead via Pd(Ar)OAc, which has no prior precedents.[40-41]

**Reaction Optimization.** We began our investigations by examining the debromo-deuteration of *N*-(4-bromobenzyl)-*N*-cyclohexylbenzamide (**1a**), a readily available electronic neutral aryl bromide. Based on prior studies,[42] we elected to evaluate $PdCl_2(amphos)_2$ [amphos = (4-(*N*, *N*-Dimethylamino)phenyl)di-tert-butyl phosphine] as the molecular Pd catalyst and **Zn1** as Lewis acid to promote the cationic Pd complex formation. We found that the deuteriation reaction was readily catalyzed by the combination of $PdCl_2(amphos)_2$ and **Zn1** in THF with moderate yield (58%, entry 2), while no product **1b** was detected without **Zn1** (entry 1). Including inorganic base KOAc to neutralize the resulting HBr led to complete conversion towards the desired product **1b**. Further experimentation revealed that KOAc alone could help drive the reaction to completion without **Zn1**, potentially broadening its applicability to users (entries 3-4). Next, we evaluated other reaction parameters to examine the generality of the catalytic system. The reaction is compatible with polar solvents such as DMAc, NMP, DMSO, $PhCF_3$, and HFIP, providing moderate to excellent yield (Table S3 in the supporting information). These solvents are particularly preferred for late-stage isotope labeling since drug candidates of interest typically have better solubilities in polar solvents.[2] Compared to KOAc, $Zn(OAc)_2$ provided better conversion towards product across various solvent environments and substrates (entries 5-6, Table S4). Switching $Zn(OAc)_2$ to NaOAc or $Zn(OTf)_2$ led to decreased yields, indicating both Zn cation and acetate are actively involved in the catalytic system (entries 7-8). Lowering the Pd loading to 1 mol% or inclusion of water did not impact the reactivity or deuterium incorporation, while Pd catalyst presence was essential for reactivity (entries 9-11). Aryl chloride **2a** was unreactive with the $PdCl_2(amphos)_2$. Ligand screening on 96 achiral commercial phosphines via high throughput experiment (HTE) uncovered the desired reactivity (Details in Table S8). Replacing the ligand with $PAd_3$ resulted in 63% yield with high D incorporation (entries 12-13). With *t*Bu-BrettPhos, we were able to achieve complete conversion to product but with diminished D enrichment (entries 14). This deuterium scrambling could be attributed to the activation of the benzylic proton located in the ligand backbone, which was observed with several phosphine ligands containing benzylic protons (Table S7 and S8). Finally, with electron-rich **L1**, the reaction proceeded in complete conversion to the product with high deuterium incorporation (entry 15).




| Entry[a] | Deviation | %Yield (1b) %[D enrichment] |
|---|---|---|
| | **1a** | |
| 1 | None | 0 |
| 2 | **Zn1** (25 mol%) | 58 [100] |
| 3 | **Zn1** (25 mol%) and KOAc 3 equiv | 100 [100] |
| 4[b] | KOAc 3 equiv | 100 [100] |
| 5 | KOAc 3 equiv in DMAc | 85 [100] |
| 6 | $Zn(OAc)_2$ 1.5 equiv in DMAc | 100 [100] |
| 7 | NaOAc 3 equiv in DMAc | 52 [100] |
| 8 | $Zn(OTf)_2$ 1.5 equiv in DMAc | 6 [100] |
| 9 | 1 mol% [Pd], $Zn(OAc)_2$ 1.5 equiv in DMAc | 100 [100] |
| 10 | 1 mol% [Pd], $Zn(OAc)_2 \cdot 2H_2O$ 1.5 equiv in DMAc | 100 [100] |
| 11 | No [Pd], $Zn(OAc)_2$ 1.5 equiv in DMAc | 0 |
| | **2a** | |
| 12 | $Zn(OAc)_2$ 1.5 equiv in DMAc | 0 |
| 13 | $Pd(OAc)_2$ and $P(Ad)_3$ instead of $PdCl_2(amphos)_2$ $Zn(OAc)_2$ 1.5 equiv in DMAc | 63 [100] |
| 14 | $Pd(OAc)_2$ and *t*Bu-BrettPhos instead of $PdCl_2(amphos)_2$, $Zn(OAc)_2$ 1.5 equiv in DMAc | 100 [46] |
| 15 | $Pd(OAc)_2$ and **L1** instead of $PdCl_2(amphos)_2$ $Zn(OAc)_2$ 1.5 equiv in DMAc | 100 [100] |

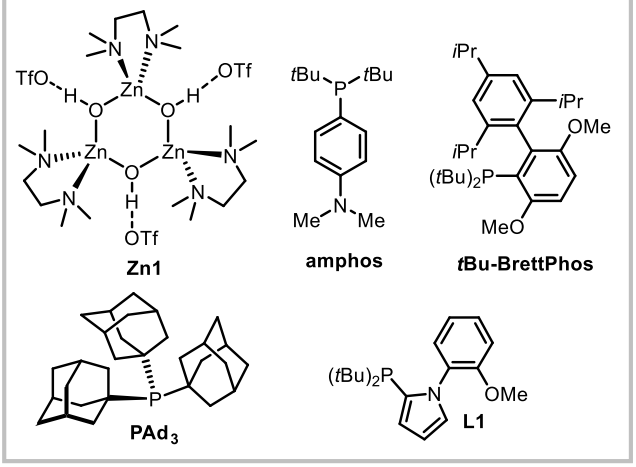


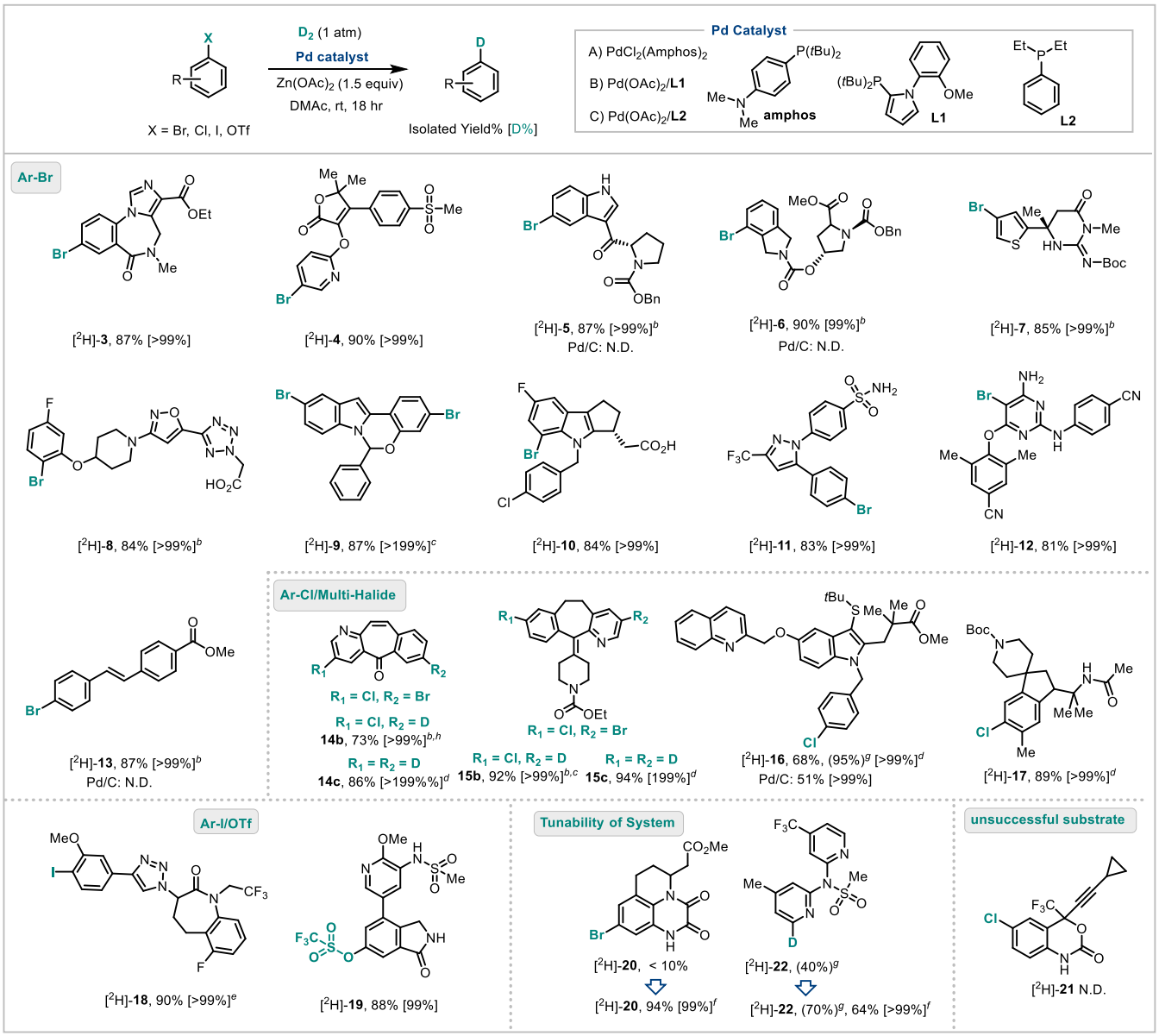

**Figure 1. Optimization Studies. [a]Reactions were conducted at a 5 µmol scale. The yield was determined via LCMS using 1,3,5-trimethoxybenezene as internal standard. [b]Reaction time is 6 hr instead of overnight.**

**Deuteration of Pharmaceuticals.** Considering the primary application in the pharmaceutical industry, we explored the generality of the homogenous palladium-catalyzed deuteration directly with functional-group dense aryl halides from our

chemistry informer library[43-46] and some pharmaceutically-relevant molecules under the optimal conditions.

We found that a broad range of functional groups were compatible with this molecular Pd catalytic system (Scheme 2). Substrates bearing heteroaromatic rings such as pyridyl (**4**), indole (**5**), thiophene (**7**), and pyrimidine (**12**) produced products in high yield (81 – 90%) with excellent D incorporation. The reaction exhibited tolerance to acidic protons present in the substrates, with **8**, **11,** and **12** being formed in excellent yields with no H/D scrambling observed. Functional groups that are sensitive to reducing conditions, such as alkene (**13**, **14**, **15**), *O*-benzyl (**5, 6**), *N*-benzyl (**10**, **16**), and cyano (**12**) were left intact under optimized conditions, with isolated yields of 73–95%.

**Scheme 2. Substrate scope for homogenous Pd-catalyzed deuteration**[a]




[a]Reactions conducted with 0.2 mmol aryl halide,1 mol% $Pd(OAc)_2$, and 2 mol% **L1**. Deuterium incorporations were reported in parentheses and determined by $^1H$ NMR integration relative to an unlabeled C–H site and corroborated by LCMS/IsoPat[2] analysis. [b]Using 1 mol% $PdCl_2(amphos)_2$ instead of $Pd(OAc)_2$/**L1**. [c]Using 2 mol% $Pd(OAc)_2$ and 4 mol% **L1**. [d]Using 10 mol% $Pd(OAc)_2$ and 20 mol% **L1**. [e]60 °C instead of rt. [f]Using **L2** instead of **L1** with 1 equiv NaOH. [g]Assay yield. [h]6 hr instead of 18 hr.

In comparison, when subjected to traditional Pd/C conditions, those substrates suffered from undesired over-reduction or bond cleavage. As a result, the complete decomposition of Cbz motifs occurred on **5** and **6,** and the stilbene group was completely reduced into alkane on **13**. Similar cleavage at quinolinyl was also observed on **16**.

By adjusting the catalyst loading and the reaction time, selective debromination of **14** and **15** was achieved, completely suppressing dechlorination to afford **14b** and **15b,** respectively. It is noteworthy that ArBr **12,** containing an aniline group, was converted smoothly to the deuterated product in high yield and complete D incorporation, while in contrast, substrates with

primary amine groups are problematic via methods reported by Ritter[39]. The reaction also showed remarkable tolerance towards steric hindrance, as evidenced by the successful formation of desired products in high yields (84–90%) even in the presence of adjacent substituted substrates (**8**, **10**, **17, 18**). Interestingly, the reaction with aryl iodide **18** proceeded slowly under the standard conditions. Elevating the reaction temperature to 60 °C boosted the yield from 68% to 96% with complete D incorporation. Moreover, this homogenous catalytic system also succeeded in the reduction of aryl triflate **19**, which was efficiently converted to the desired product under standard debromodeuteration conditions. This provides a complementary deoxygenation method with enhanced efficiency and improved functional group tolerance.

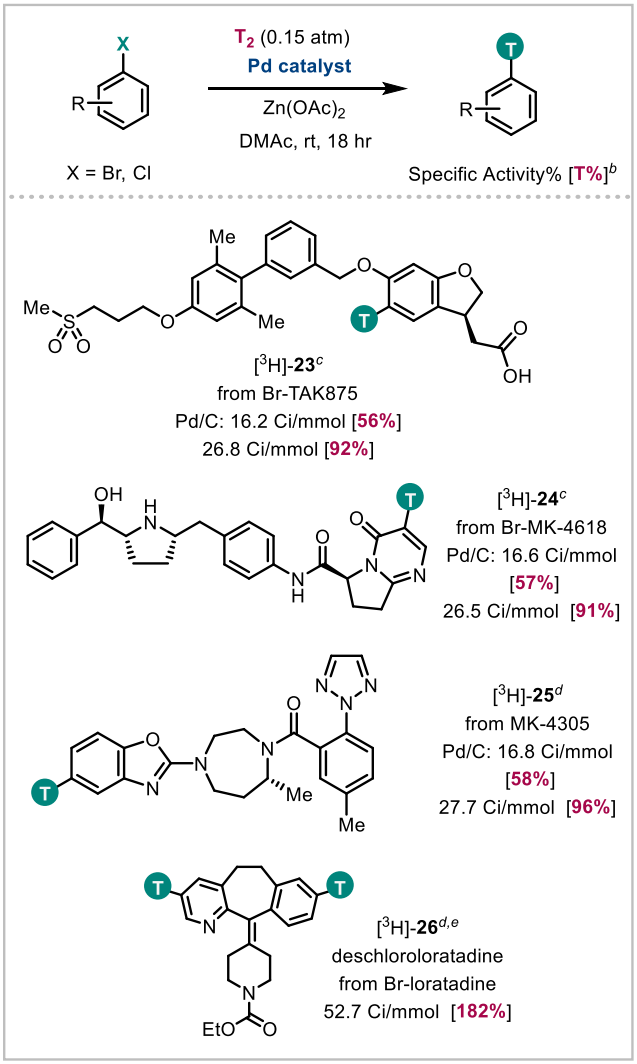
Taking advantage of the exceptional tunability of molecular Pd catalysts and the significant advancements in phosphine ligand development over the years[47-48], this methodology exhibited excellent flexibility for reaction optimizations. In situations where transformations were initially unsuccessful, they could be effectively enabled through simple ligand modification and the addition of an inorganic base. For instance, substrates containing α,β-dione motifs (**20**), and α-pyridyl halide (**22**) experienced low conversion under standard conditions, plausibly due to their chelating properties. However, by switching the ligand from **L1** to **L2**, the yield was significantly improved from less than 10% to 94% for **20** and from 40% to 70% for **22**, respectively.

A current limitation of the method is the dechlorination of substrates containing an alkynylcyclopropyl group (**21**), which unfortunately resulted in a mixture of byproducts from over-reduction and ring-opening.

Overall, the homogenous dehalogenative deuterations demonstrated generality for diverse aryl halides and pseudohalides with varying electronic and steric properties. Notably, these reactions consistently provided the quantitative level of D incorporations and high yields and displayed remarkable tolerance toward a broad range of functional groups. Besides the reducible groups mentioned before, many of these functional groups are commonly encountered in medicinal chemistry, such as *N*-containing heterocycles, sulfonamides, amides, carbamates, amines, and carboxylic acids.

**Tritiation of Pharmaceuticals.** We were particularly intrigued by the potential of the homogenous palladium system in dehalogenative tritiation, as it would offer the advantage of predictable high SA. Unlike deuteration reactions, tritiations typically occur on a micromolar scale under a low-pressure $T_2$ gas atmosphere (0.15 atm). To our delight, we found tritiations proceeded smoothly across a range of bromo- and chloro-substituted pharmaceutical drug molecules. Remarkably, this approach achieved an impressive tritium incorporation level of over 91% tritium per halogen atom (1 T = 29 Ci/mmol, **Scheme 3**). TAK-875 (Fasiglifam), an orally available GPR40 agonist that has reached clinical phase III, posed a challenge for tritiation using existing HIE methods. Indeed, a dry Pd/C catalyzed debromotritiation was performed using 2.6 Ci $T_2$ gas, but it only yielded [$^3$H]-**23** in a SA of 16.2 Ci/mmol.[49] This result aligns with the trend for aryl bromides illustrated in **Scheme 1B**. To showcase the capabilities of our homogenous palladium system, we compared the reactivity of the same aryl bromide under the homogenous conditions with 1 Ci of $T_2$ gas. As anticipated, use of our conditions resulted in a significant improvement, boosting the SA of [$^3$H]-**23** by 65% to 26.8 Ci/mmol. Moreover, it offered a higher radiochemical yield (RCY) and reduced radioactive waste drastically. We achieved similar success with MK-4618, labeling it with tritium using the debromotritiation protocol, yielding a much higher SA ([$^3$H]-**24**, 26.5 Ci/mmol) compared to the reported data using standard Pd/C chemistry.[50] The homogenous system also allowed for the tritiation of aryl chlorides with high specific activities. MK-4305 was dechlorotritiated to afford [$^3$H]-**25** with a SA of 27.7 Ci/mmol, dramatically surpassing the 16.8 Ci/mmol obtained via the heterogenous catalysis. Additionally, reductive tritiation of Br-loratadine produced the Br/Cl-double reduced tritiation product [$^3$H]-**26** at an elevated temperature, delivering a SA of 52.7 Ci/mmol meeting the SA requirement for receptor binding studies. Overall, this homogenous palladium catalytic system showed remarkable reactivity with low-pressure tritium gas, offering a predictable high SA for readily available bromo- and chloro-substituted drug-like molecules.

**Scheme 3. Homogenous Pd-catalyzed tritiation of pharmaceuticals**[a]



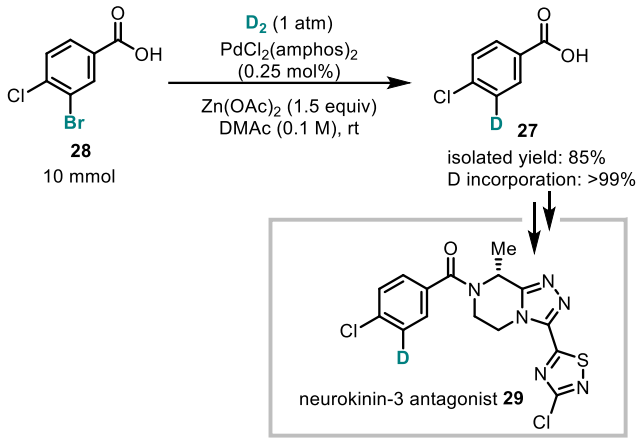

[a]Reactions conducted with 1.9–3.3 μmol aryl halides, 10 mol% Pd catalyst, 1.5 equiv of $Zn(OAc)_2$, and 1 Ci $T_2$ (0.15 atm). [b]Tritium incorporations were reported in parentheses and determined by LCMS/IsoPat[2] analysis, and labeled sites were confirmed by $^3$H NMR spectroscopy. [c]Using 10 mol% $PdCl_2$(amphos)$_2$. [d]Using10 mol% $Pd(OAc)_2$ and 20 mol% **L1**. [e]60 °C instead of rt.

**Applications in deuterium drug synthesis.** The replacement of hydrogen atoms with deuterium isotopes in drug molecules has been extensively investigated in medicinal chemistry in recent years. This strategy holds immense potential and offers multiple advantages. Precise deuteration at specific metabolic sites can lead to improvements in pharmacokinetic and toxicity profiles, reducing dosing frequency and enhancing oral bioavailability in the clinic. Additionally, it provides an opportunity to stabilize stereocenters or discover drug molecules with novel mechanisms of action. Notably, the FDA has approved two deuterium drugs, deutetrabenzaine[51] and deucravacitinib[52-53]. This underscores the growing interest in developing efficient, practical, widely applicable, and scalable deuteration methods that ensure precise and complete deuterium incorporation.

As mentioned above, the most widely employed reaction for deuterated arenes/heteroarenes synthesis is dehalogenative deuteration using heterogeneous catalysts. However, practical implementation of this method often requires high catalyst loadings, deuterated solvents or reagents, and rigorous drying and pre-deuteration protocols to achieve satisfactory deuterium incorporation levels. Consequently, scaling up these processes becomes challenging and less feasible.[24-25]

To demonstrate the capability of our newly developed homogenous palladium catalytic system, we performed a gram-scale debromodeuteration of 3-bromo-4-chlorobenzoic acid (**Scheme 4**). This pivotal transformation is to prepare deuterated intermediate **27** required for the synthesis of a neurokinin-3 receptor antagonist **29**.[54] With 0.25 mol% [Pd] and DMAc (0.1 M), the reaction proceeded smoothly to afford the corresponding 4-chlorobenzoic-3-*d* acid **27** in a high isolated yield (85%), along with complete D incorporation and exclusive site selectivity.

**Scheme 4. Gram-scale debromonative deuteration to prepare essential intermediate 27 for deuterium drug 29.**




**Mechanistic studies.** To gain a deeper insight into the mechanism, we conducted a series of preliminary mechanistic studies to probe the active palladium intermediates involved in the reaction. We chose $PAd_3$ (tri-adamantylphosphine) for further stoichiometric studies owing to its favorable reactivity (**Figure 1**, entry 13), along with the thorough characterization of the corresponding Pd complexes in prior research.[55-57] Previous reports identified cationic $[P(Ad)_3Pd–Ar]^+$ (**Pd3**), synthesized from $[P(Ad)_3PdArCl$ (**Pd1**) and $AgBF_4$, as the active intermediate that facilitates transmetallation.[56] However, intriguingly, when we conducted the synthesis under the same condition using $Zn(OAc)_2$ instead of $AgBF_4$, NMR analysis revealed no formation of the cationic **Pd3**. Instead, a new intermediate, PdArOAc (**Pd2**), was observed in a yield of 50% within 30 seconds (**Figure 2A**, S41-42). To gather direct evidence of the catalyst resting state, we employed NMR spectroscopy to monitor the catalytic reaction progress using **Pd4** as the catalyst and 1-bromo-4-fluorobenzene as the substrate (**Figure 2B**). Notably, the characteristic NMR signals of **Pd2** were detected both before and after the introduction of $D_2$ gas into the J. Young NMR tube. This observation suggests that a rapid conversion from **Pd4** to **Pd2** occurred in the presence of $Zn(OAc)_2$ in DMAc-$d_9$. Under $D_2$ atmosphere, the signal intensity of **Pd2** remained constant, while the signals of 1-bromo-4-fluorobenzene gradually diminished and the deuterated product started accumulating. This behavior strongly suggests that **Pd2** is the catalyst resting state (Figure S33-38). Moreover, when subjected to $D_2$, **Pd2** readily reacted with $D_2$, resulting in 90% consumption in 15 minutes (**Figure 2C**, S43).

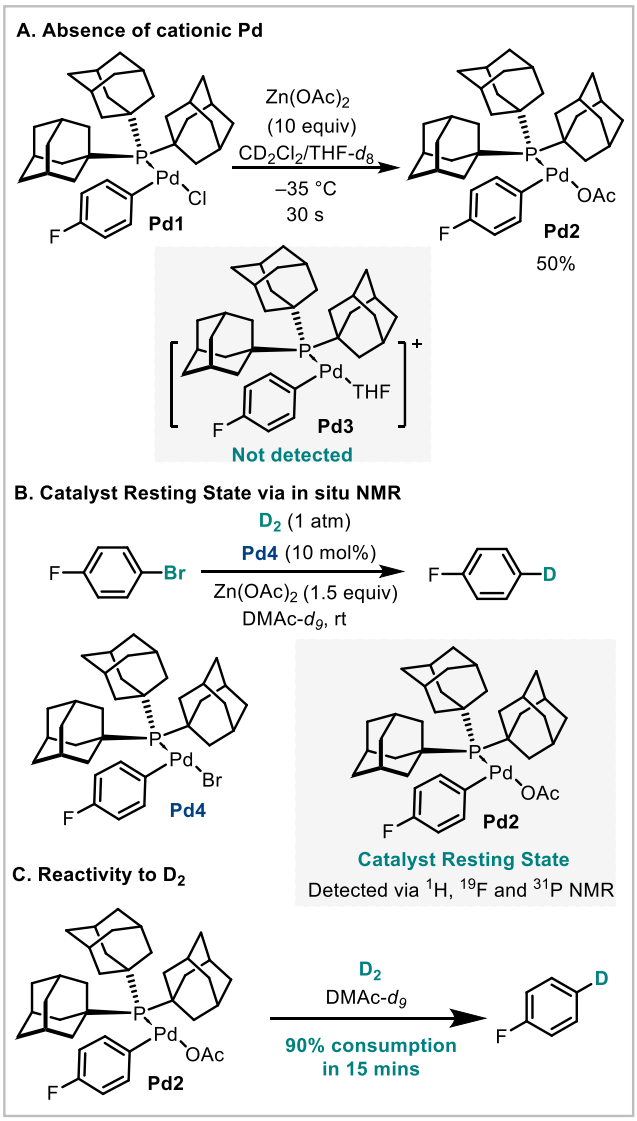



**Figure 2. Mechanistic investigations.**

Taken together, these findings are consistent with the proposed catalytic cycle (**Figure 3**). The reaction begins with the oxidative addition of aryl halides to Pd(0), forming Pd(II)ArX. Subsequently, rapid ligand exchange occurs with $Zn(OAc)_2$.

This leads to the formation of PdArOAc, the catalyst resting state. PdArOAc is capable of activating the $D_2$ bond, resulting in the Pd(II)−D intermediate. This Pd(II)−D species then undergoes a facile reductive elimination to form the desired dehalogenative arene product. The exact pathway of $D_2$ activation by PdArOAc is still under investigation, whereas the heterolytic $D_2$ activation assisted by carboxylate shown in **Figure 3** as the proposed transitional state has been observed in Ni[58], Ru[59], Pd[41], and Co[60] hydrogenation activation.

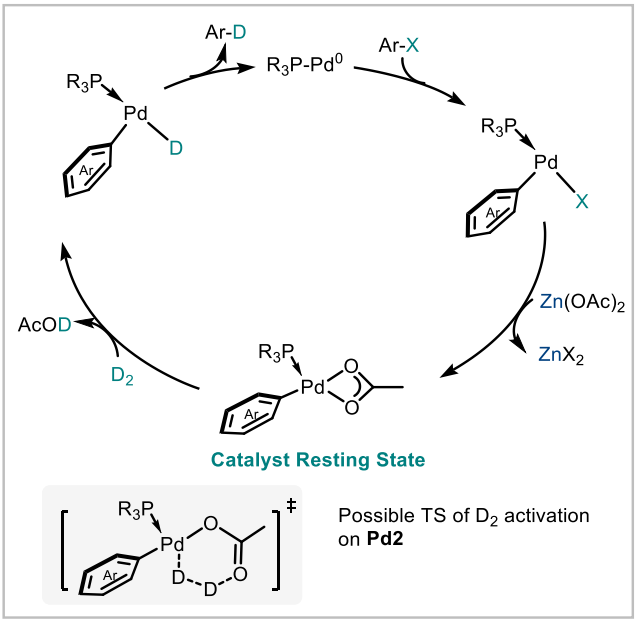



**Figure 3. Proposed mechanism for Pd-catalyzed dehalogenative deuteration of aryl halides and possible transitional state for $D_2$ activation.**

In summary, we have developed a novel homogenous palladium-catalyzed dehalogenative deuteration and tritiation of aryl halides with zinc acetate as a critical additive. This reaction demonstrated excellent tolerance towards various functional groups and exhibited higher hydrogen isotope incorporation than existing heterogeneous catalytic systems. Notably, the tritiation of pharmaceutical compounds achieved high SA per halogen atom (26.5-27.7 Ci/mmol), addressing a long-standing limitation in Pd/C chemistry for aryl bromide and chloride substrates. The gram-scale reaction showed the significant potential of this reaction in the synthesizing large quantities of deuterium-containing API molecules. Preliminary mechanistic studies suggest a pathway involving a PdArOAc intermediate as the catalyst resting state. Overall, this homogenous palladium-catalyzed deuteration/tritiation of aryl halides offers a valuable synthetic addition to the state-of-the-art methods for deuterium/tritium labeling of arenes and heteroarenes. This innovation has potential to change the practice of dehalogenative deuteration and tritiation in the realm of hydrogen isotope labeling.

## ASSOCIATED CONTENT

Supporting Information.
The Supporting Information is available free of charge via the Internet at http://pubs.acs.org.
Detailed experimental procedures; characterization data, such as NMR, Mass, and LC spectra

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### Notes

The authors declare no competing financial interest.

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## ABBREVIATIONS

| | |
|---|---|
| API | active pharmaceutical ingredient |
| HIE | hydrogen isotope exchange |
| HTE | high throughput experimentation |
| LSF | late-stage functionalization |
| RCY | radiochemical yield |
| SA | specific activity |
| TT | thianthrenium |

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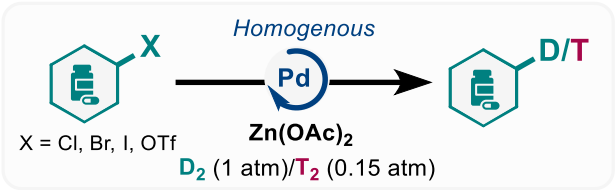
SYNOPSIS TOC




- high D/T incorporation
- suitable method for scaling up
- exclusive site selectivity
- tunable to haloselectivity
- tolerance to C=X, O/N-benzyl, -CN, -$NH_2$ etc