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Synthesis of Multideuterated (Hetero)aryl Bromides by Ag(I)-Catalyzed H/D Exchange

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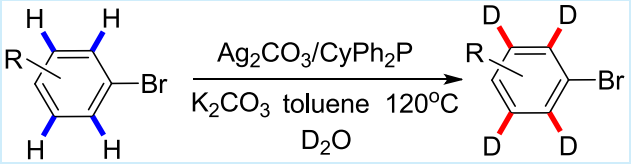
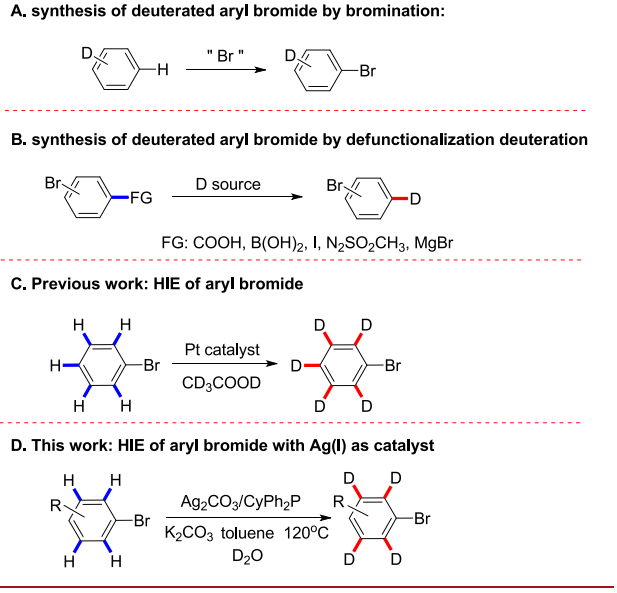
ABSTRACT: Deterium-labeled (hetero)aryl bromide is one of the most widespread applicable motifs to achieve important deuterated architectures for various scientific applications. Traditionally, these deterium-labeled (hetero)aryl bromides are commonly prepared via multistep syntheses. Herein, we disclose a direct H/D exchange protocol for deuteration of (hetero)aryl bromides using Ag_2CO_3 as catalyst and D_2O as deuterium source. This protocol is highly efficient, simply manipulated, and appliable for deuterium-labeling of over 55 (hetero)aryl bromides including bioactive druglike molecules and key intermediates of functional materials. In addition, this method showed distinguishing site-selectivity toward the existing transition-metal-catalyzed HIE process, leading to multideuterated (hetero)aryl bromides in one step.



The increasing applications of deuterium-labeled compounds in various scientific fields have recently attracted increased attention.[1] In the pharmaceutical industry, deuterium-labeling has been established as a powerful tool to explore the ADME properties of active pharmaceutical ingredients.[2] In material science, deuterated and nondeuterated optoelectronic materials could show different behavior in crystallization, resulting in a great impact on lighting quantum yield and device efficiency.[3] In organic chemistry, the kinetic isotope effect experiment is commonly applied in the elucidation of reaction mechanism.[4] In chemical analysis, selective deuterated compounds are ideal standards for mass spectrum analysis of environmental pollutants and residual pesticides.[5]

As one of the most important substrates in organic chemistry, aryl bromides were widely used as synthetic building blocks enabling quick access to a wide array of bioactive molecules, organic materials, and polymers via the versatile cutting-edge transformations of C−Br bond.[6] Traditionally, deuterated aryl bromides were commonly prepared from bromination of the corresponding deuterated aryl precursors (Scheme 1A).[7] Although a range of deuterated aryl bromides can be prepared by this method, the high cost, due to multistep synthetic route beginning from the expensive deuterated precursors, restricted its broad use. The alternative way to prepare deuterated aryl bromides relied on a defunctionalisation-deuteration stratergy.[8] However, the preinstallation of leaving groups disadvantaged further application of these protocols in deuterium-labeling of complicated molecules (Scheme 1B). Direct hydrogen isotope exchange (HIE) is considered to be the most straightforward method for quick access to deuterated arenes.[9] Recently, direct HIE reactions with transition metals including Ir,[10] Pd,[11] Ru,[12] Pt,[13] Fe,[14] Ni,[15] and Co[16] as catalyst have been well explored as a prevalent method for selective deuterium-labeling of aromatic rings (Scheme 1C). Despite many efforts on the extension of substrate scope, the reported transition-metal-catalyzed H/D exchange protocols still relied on the use of directing groups

Scheme 1. Methods for Synthesis of Deuterium-Labeled Aryl Bromide



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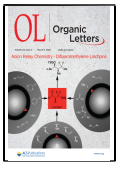

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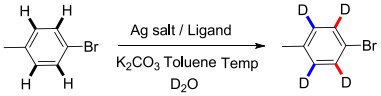
containing an N or O atom to assist H/D exchange processes and to control site-selectivity. Direct H/D exchange of aryl bromides is still a great challenge, mainly due to their relatively lower reactivity of C−H bond and fragile nature of C−Br bond.[17] For example, complete debromination was observed in H/D exchange process with Pd/C as catalyst.[18] Although H/D exchange of bromobenzene with CD_3COOD as deuterium source can be achieved by a cationic ligand coordinated platinum complex as catalyst,[19] direct deuteration of substrates other than simple bromobenzene was still unexplored. Therefore, a general method for direct H/D exchange of aryl bromide with broad substrate scope is still in high demand.

Our group is devoted to developing new methods for synthesis of deuterated organic compounds.[20] Recently, we have developed a silver salt catalyzed H/D exchange reaction for deuteration of five-membered heterocycles and fluoroarenes.[21] However, due to their relatively lower reactivity, the direct C−H activation of aryl bromides with silver salt as catalyst is still unknown.[22] In this paper, we disclose an efficient, convenient, and catalytic method for H/D exchange of aryl bromide with silver salt as catalyst and heavy water as deuterium source. The reaction showed broad substrate scope, enabling quick access to many valuable deuterated aryl bromides, which are commonly complicated to prepare with other methods.

Our initial efforts toward H/D exchange of aryl bromide commenced with the reaction of 4-bromotoluene and heavy water employing the combination of silver carbonate and phosphine ligands as catalyst. After thorough screening of ligands, cyclohexyldiphenylphosphine ($CyPh_2P$) was found to be the best to promote the HIE process, providing the product with 0.77 deuterium incorporation (entries 1−8, Table 1). Other silver salts were also tested, and none of them gave better results than silver carbonate, which is consistent with our previous observations (entries 9−11, Table 1).[21a] We then screened the solvents and found toluene is the best choice of solvent (see table s1). Further investigation of solvent indicated that concentration played an important role in the H/D exchange process, and a better result of 1.06 deuterium incorporation was obtained by using 0.1 mL of toluene as solvent (entries 12−14, Table 1). Increasing the amount of heavy water to 20 equiv can obviously improve deuterium incorporation (entry 15, Table 1). However, continuously increasing the amount of heavy water never gave better results, probably due to the poor solubility of substrates in water (see Table S2). Interestingly, by analyzing the ^{1}H NMR spectrum of the isolated product, we found that this H/D exchange reaction showed distinguishing site selectivity with 1.6 deuterium incorporation at the *ortho*-position and 0.4 deuterium incorporation at the *meta*-position of the bromide group. In addition, we found that conducting the reaction at higher temperature can further increase the level of deuterium incorporation, affording 3.10 deuterium incorporation at 120 °C (entries 16 and 17, Table 1). Other deuterium sources such as $CDCl_3$, CD_3CN, and CD_3OD are demonstrated to be much less efficient (see Table S2). Therefore, the optimal conditions were established with Ag_2CO_3/$CyPh_2P$ as catalyst and D_2O/toluene as cosolvent at 120 °C.

Table 1. Reaction Optimization



1a 2a

entry[a]	Ag salt	ligand	toluene	D incorporation[b]
1	Ag_2CO_3	Ph_3P	1 mL	0.06
2	Ag_2CO_3	Sphos	1 mL	0.34
3	Ag_2CO_3	DavePhos	1 mL	0.64
4	Ag_2CO_3	JohnPhos	1 mL	0.42
5	Ag_2CO_3	MePhos	1 mL	0.60
6	Ag_2CO_3	$CyPh_2P$	1 mL	0.77
7	Ag_2CO_3	Cy_3P	1 mL	0.09
8	Ag_2CO_3	Cy_2PhP	1 mL	0.09
9	Ag_2O	$CyPh_2P$	1 mL	0.09
10	AgOAc	$CyPh_2P$	1 mL	0.04
11	CF_3COOAg	$CyPh_2P$	1 mL	0.12
12	Ag_2CO_3	$CyPh_2P$	0.5 mL	0.66
13	Ag_2CO_3	$CyPh_2P$	0.2 mL	0.86
14	Ag_2CO_3	$CyPh_2P$	0.1 mL	1.06
15[c]	Ag_2CO_3	$CyPh_2P$	0.1 mL	1.86
16[c,d]	Ag_2CO_3	$CyPh_2P$	0.1 mL	2.86
17[c,e]	Ag_2CO_3	$CyPh_2P$	0.1 mL	3.10

[a]The reaction was conducted on 1 mmol of 1a, 10 mmol of D_2O, 0.2 mmol of Ag salt, and 0.5 mmol of ligand in toluene at 80 °C, 12 h. [b]Determined by GC−MS. [c]20 mmol of D_2O was used. [d]At 100 °C. [e]At 120 °C.

With the optimal reaction conditions in hand, we set out to explore the generality of this method with respect to functionalized aryl bromide. As shown in Scheme 2, the *para*-substituted bromobenzenes showed excellent H/D exchange efficiency, affording products with deuterium incorporation from 83% to 92% at the *ortho*-position (**2aa**−**2aj**). When the *para*-position of bromobenzene was substituted by alkyl, phenyl, alkyne, amine or carbonyl groups, the H/D exchange reaction showed preferential orientation toward *ortho*-position over *meta*-position, affording products with deuterium incorporation of 14% to 79% at *meta*-position (**2aa**−**2af**). On the other hand, the bromobenzenes substituted by an alkoxyl group at *para*-position showed high level of deuterium incorporation at both *ortho*- and *meta*-positions (**2ag**−**2aj**). These results suggested that deuterium incorporation at the *meta*-position could be controlled by steric effects and/or electronic effects. On the basis of our results and the reported reference, the selectivity of this H/D exchange reaction may controlled by the acidity of the C−H bond, in which H/D exchange occurred more easily adjacent to electronegative elements. The bromobenzenes with *ortho*-substitution were then tested, and we found the H/D exchange will occur only at the *ortho*- and *meta*-position of the bromide group, affording products with no deuterium incorporation at the *para*-position of bromide (**2ak**−**2am**). To the best of our knowledge, the H/D exchange process showing this special kind of site selectivity has been rarely observed,[23] which could be a complementary strategy for producing valuable multi-deuterated aryl bromides. We next examined aryl bromides with *meta*-substitutions as starting materials, which also showed a high level of deuterium incorporation at the *ortho*-position and a moderate or good level of deuterium incorporation at the *meta*-position (**2an**−**2aq**). In addition, brominated polyarenes including 1-bromonaphthalene, 2-bromonaphthalene, 2-bromonathraquinone, and 2-bromo-9,9-dimethylfluorene all showed good H/D exchange efficiency (**2ar**−**2au**). The H/D exchange of 9-bromophenanthrene (**2av**) was observed selectively at the *ortho*-position of bromide

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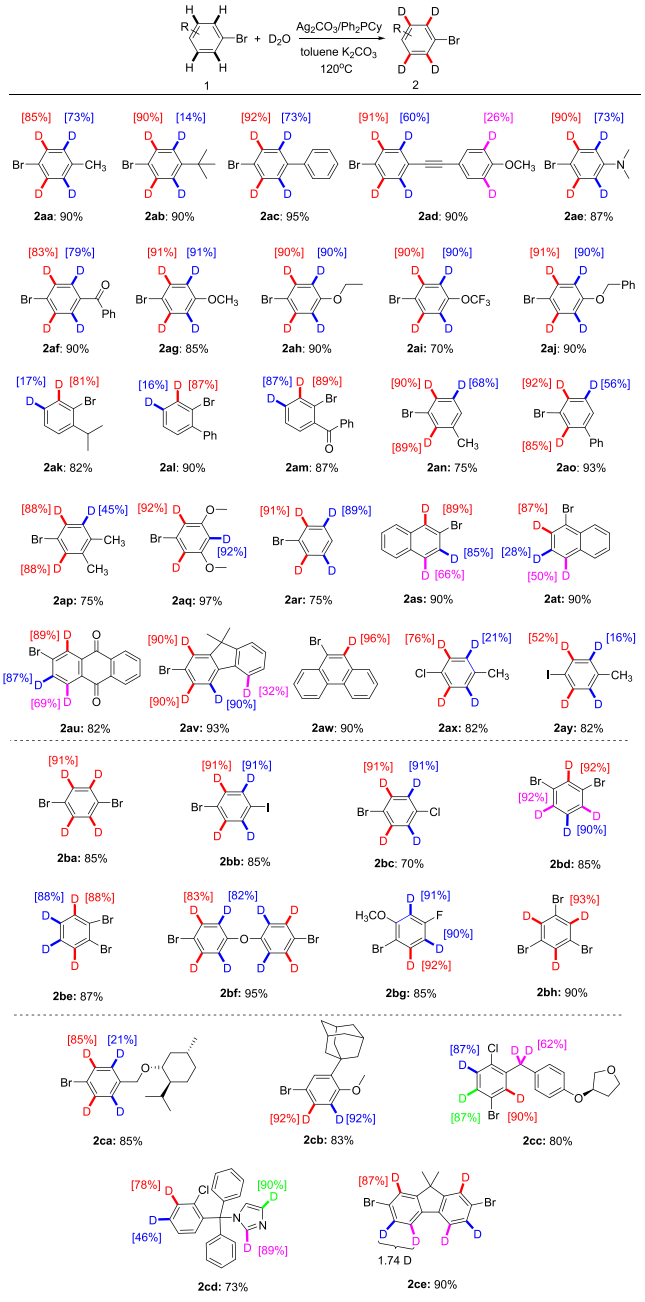
Scheme 2. Deuteration of Brominated Arenes[a]

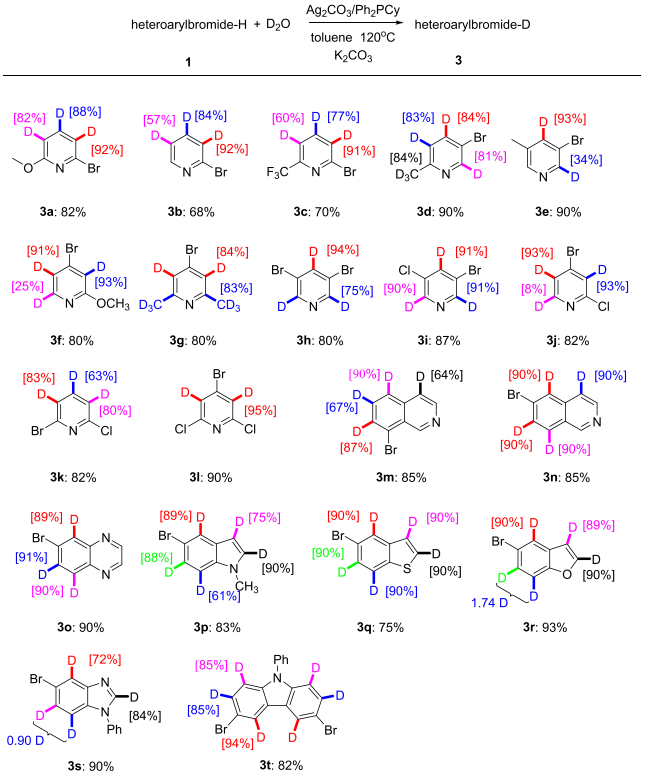


[a]The reaction was conducted with compound **1** (1 mmol), D_2O (20 mmol), Ag_2CO_3 (0.2 mmol), $CyPh_2P$ (0.5 mmol) in 0.1 mL of toluene at 120 °C for 24 h; deuterium incorporation was estimated by ^1H NMR spectrum; isolated yield.

with deuterium incorporation of 96%. The high *ortho*-position selectivity could be explained by its high reactivity toward C−H activation, which has been well reported previously.[24] Moreover, we found 4-chlorotoluene and 4-iodotoluene are also good substrates for this H/D exchange reaction, providing the products with the same site-selectivity but less efficiency than 4-bromotoluene (**2aw**−**2ax**).[25] With multihalogenated arenes as starting materials, fully deuterated arenes could be easily prepared under the optimal condition (**2ba**−**2bh**). The products with deuterium incorporation of 82%−93% at every position were obtained. To further elaborate the utility of this transformation, deuteration of key intermediates of drugs and functional materials as well as natural product derivatives have been examined. First, introducing deuterium into menthol derivatives and clotrimazole were successfully achieved (**2ca** and **2 cd**). Deuterated key intermediates of adapalene and empagliflozin (**2cb** and **2cc**) were readily synthesized from the corresponding bromide precursors in excellent level of deuterium incorporation. Furthermore, the important intermediate for organic/polymeric phosphorescence material, 2,7-dibromo-9,9-dimethylfluorene,[26] was a good substrate for H/D exchange, leading to fully deuterated product with excellent level of deuterium incorporation (**2ce**).

The successful deuteration of aryl bromides promoted us to investigate deuterium incorporation of heteroaryl bromides. We first examined the H/D exchange of brominated nitrogen-containing heteroarenes because nitrogen-containing heteroarenes are common structure motifs in functional materials and bioactive compounds.[27] As shown in Scheme 3, monobromi-

Scheme 3. Deuteration of Brominated Heteroarenes[a]



[a]The reaction was conducted with compound **1** (1 mmol), D_2O (20 mmol), Ag_2CO_3 (0.2 mmol), and $CyPh_2P$ (0.5 mmol) in 0.1 mL of toluene at 120 °C for 24 h; deuterium incorporation was estimated by ^1H NMR spectrum; isolated yield.

nated pyridine derivatives are good substrates for H/D exchange, leading to products with multiple deuterium incorporation (**3a**−**3g**). In addition, when the methyl group was substituted at the *ortho*-position of pyridine, H/D exchange of the methyl group was also observed (**3d** and **3g**). It could be explained by their relatively higher acidity,[28] which was believed to play important role in Ag(I)-catalyzed H/D exchange reaction. The multihalogenated pyridine derivatives provided higher reactivity for H/D exchange, leading to fully deuterated pyridines in most cases (**3h**−**3l**). Brominated isoquinolines are also examined, providing good to excellent level of deuterium incorporation at multiple positions

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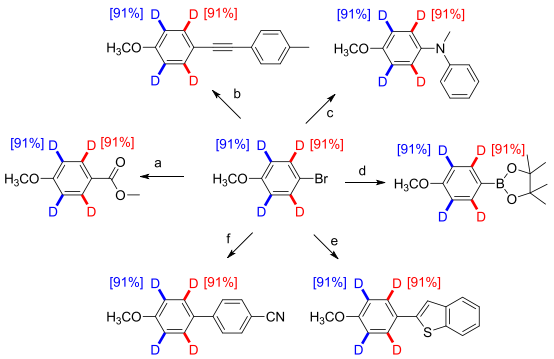
(**3m** and **3n**). Deuteration of 6-bromoquinoxaline led to installation of three deuterium atoms in the phenyl ring (**3o**). Besides the electro-deficient heteroarenes, H/D exchange of electron-rich brominated five-membered heterocycles was further examined. Fully deuterated products with a high level of deuterium incorporation were easily obtained (**3p**−**3t**). In most cases, this H/D exchange protocol can introduce multiple deuterium atoms in one step, which may find wide applications in development of novel functional materials and synthesis of standards for MS analysis.[3,5]

To further demonstrate the usefulness of this Ag_2CO_3-catalyzed H/D exchange protocol, we conducted the transformation of the C−Br bond to build up other useful deuterated building blocks (Scheme 4). Deuteration of **1ag**

Scheme 4. Transformation of C−Br Bond

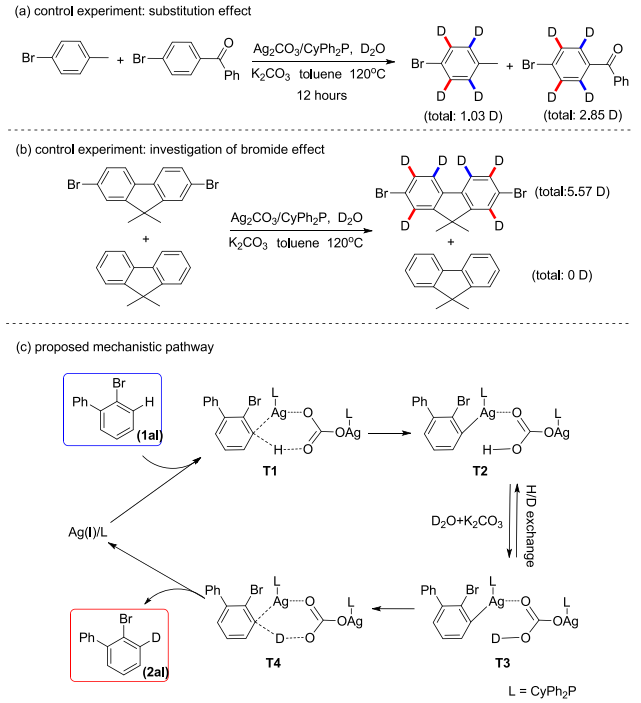


[a]The reaction was conducted with **2ag** (0.5 mmol), potassium oxalate (0.75 mmol), $PdCl_2$ (0.02 mmol), and dppp (0.03 mmol) in NMP (1 mL) at 150 °C under N_2. [b]The reaction was conducted with **2ag** (1 mmol), 4- ethynyltoluene (1.5 mmol), $Pd(OAc)_2$ (0.02 mmol), PPh_3 (0.2 mmol), and K_2CO_3 (1.5 mmol) in DMSO (5 mL) at 80 °C under N_2. [c]The reaction was conducted with **2ag** (1 mmol), *N*-methylaniline (1.2 mmol), $Pd(OAc)_2$ (0.01 mmol), Ruphos (0.2 mmol), and NaO^{t}Bu(1.5 mmol) at 110 °C under N_2. [d]The reaction was conducted with **2ag** (1 mmol), bis(pinacolato)diboron (1.2 mmol), Pd(dppf)Cl_2 (0.02 mmol), and KOAc (3 mmol) in DMSO (5 mL) at 80 °C under N_2. [e]The reaction was conducted with **2ag** (1.5 mmol), benzothiophene (1 mmol), $Pd_2(dba)_3$ (0.005 mmol), Sphos (0.01 mmol), and NaOtBu (3 mmol) in *o*-xylene (2 mL) at 140 °C under N_2. [f]The reaction was conducted with **2ag** (1.0 mmol), 4-cyanobenzoic acid (1.5 mmol), $Pd(PPh)_4$ (0.05 mmol), and KOAc (5 mmol) in toluene/H_2O (4/2 mL) at 140 °C under N_2.

(1.86 g, 10 mmol) afforded **2ag** in 90% yield and 92% deuterium incorporation at both the *ortho*- and *meta*-positions, suggesting this H/D exchange protocol is readily scalable. As shown in Scheme 4, the C−Br bond can be converted to functional groups such as ester, amine, and boronic ester. The cross-coupling of C−Br with different partners can introduce aryl, heteroaryl and alkyne groups into the original deuterated phenyl ring. In addition, nearly no loss of deuterium incorporation was observed in these transformations.

With the attempt to gain more insight into the reaction mechanism, a series of control experiments have been performed (Scheme 5). First, a mechanism involving free radicals should be ruled out, due to no negative effect with radical inhibitor TEMPO as additive. Second, the one-pot competitive reaction showed 4-bromobenzophenone is more reactive than 4-bromotoluene toward H/D exchange, which suggested the reaction may not follow an S_EAr pathway (Scheme 5a). Third, the one-pot competitive reaction between

Scheme 5. Control Experiments and Proposed Mechanism of Ag_2CO_3-Catalyzed HIE



9-phenylcarbazole and 2,7-dibromo-9-phenylcarbazole showed a significant reactive difference, which indicated that bromide group is essential for this H/D exchange process (Scheme 5b). On the basis of these experiments, we proposed a mechanistic pathway as follows. The phosphine ligand coordinated silver salt promoted C−H bond cleavage of **1al**, which was followed by H/D exchange between intermediate T2 and heavy water to produce deuterated intermediate T3. Finally, deuterated aryl bromide (**2al**) will generate from transformation of deuterium to aryl ring and release of silver salt.

In summary, a convenient approach for direct incorporation of deuterium into brominated (hetero)arenes with Ag_2CO_3 as catalyst has been disclosed. A good range of (hetero)arenes, including brominated benzene, pyridine, quinoline, isoquinoline, indole, benzothiophine, benzofuran, and benzoimizole, have been demonstrated to be good substrates. The distinguishing site-selectivity of this H/D exchange reaction allowed this method to prepare multideuterated organic compounds, which is extremely important in preparation of standards for MS analysis. In addition, although aryl bromide has been widely applied in synthesis of functional material and drug molecules, the direct C−H activation of aryl bromide is rarely reported. Our result demonstrated that C−H bond cleavage of brominated (hetero)arenes by the assistant of silver salt is feasible, which paves the way to functionalize brominated arenes via the direct C−H bond activation route.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04139.

Experimental procedures, spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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