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# Silver-catalyzed regioselective deuteration of (hetero)arenes and $\alpha$ -deuteration of 2-alkyl azaarenes†

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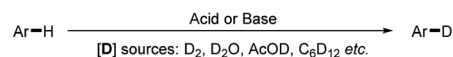
A simple silver-catalyzed regioselective deuteration of (hetero)arenes and  $\alpha$ -deuteration of 2-alkyl azaarenes has been described. This strategy provides an efficient and practical avenue to access various deuterated electron-rich arenes, azaarenes and  $\alpha$ -deuterated 2-alkyl azaarenes with good to excellent deuterium incorporation utilizing D<sub>2</sub>O as the source of deuterium atoms.

Deuterium-labelled organic compounds are of great interest and importance, as they are widely used as internal standards in analytical chemistry,<sup>1</sup> tools for elucidation of reaction mechanisms,<sup>2</sup> metabolic or pharmacokinetic probes,<sup>3</sup> and as biologically active compounds and pharmaceuticals.<sup>4</sup> Indeed, the first deuterated drug, deutetrabenazine, which is recognized as a different orphan drug for the treatment of chorea *versus* tetrabenazine, was approved by the US Food and Drug Administration in April 2017. As a result, the development of efficient and selective routes for the synthesis of deuterium labeled organic compounds is a subject of increasing interest. Among possible approaches to incorporate deuterium atoms into an organic molecule,<sup>5</sup> the H/D exchange reaction, which enables the direct deuterium labelling of the desired target molecule without the need to prefunctionalize the starting materials, represents the most straightforward and atom-efficient method. In recent years, extensive studies on H/D exchange reactions of aromatic compounds have been reported, including acid/base promoted pH-dependent H/D exchange reactions of electronically activated aromatic compounds<sup>6</sup> (Scheme 1a) and transition metal catalyzed site-selective H/D exchange reactions<sup>7</sup> (Scheme 1b). Among these, transition-metal-catalyzed reactions have gained significant momentum because these catalysts can control the site selectivity of H/D exchange reactions. However, the required ligands, the introduction of directing groups and/or the complexity of catalyst synthesis may not be readily accessible or economically viable. Therefore, there remains room to develop a simple, cost efficient and universal deuteration strategy with broad substrate scope, especially in view of

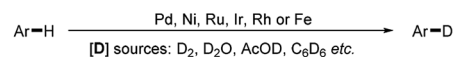
the growing demand for deuterium-labelled compounds in synthetic chemistry and pharmaceutical industry.

In past decades, silver has demonstrated their high efficiency as special mild Lewis acids, becoming catalysts of first choice for many types of catalytic reactions generally performed under mild reaction conditions and through experimentally simple procedures.<sup>8</sup> However, despite considerable progress, silver-catalyzed selective H/D exchange reaction has remained much less explored to date.<sup>9</sup> Quite recently, Huang reported an efficient Ag<sub>2</sub>CO<sub>3</sub>-catalyzed H/D exchange of five-membered heteroarenes using D<sub>2</sub>O as deuterium source at ambient temperature, but external base such as 1 equiv. of K<sub>2</sub>CO<sub>3</sub> and a phosphine ligand were still needed.<sup>9b</sup> We here developed a practical and selective silver-catalyzed deuteration of (hetero)arenes and  $\alpha$ -deuteration of 2-alkyl azaarenes utilizing D<sub>2</sub>O as the source of deuterium atom under mild neutral conditions that does not require any other additives (Scheme 1c). This protocol represents a practical and efficient method of silver-catalyzed regioselective H/D exchange reaction under mild

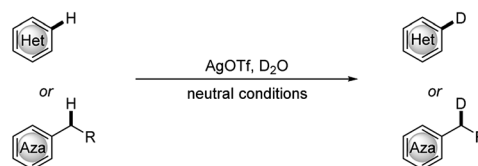
### a) Acid/base promoted deuteration of aromatic compounds (pH-dependence)



### b) Transition metals catalyzed deuteration of aromatic compounds (C-H activation)



### c) Silver-catalyzed regioselective deuteration of (hetero)arenes (This work)



Scheme 1 Selective H/D exchange reactions.

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neutral conditions, efficiently affording a wide range of deuterated electron-rich arenes, azaarenes and  $\alpha$ -deuterated 2-alkyl azaarenes through experimentally simple procedures.

Initially, we began our studies by examining the model deuteration of 1,2,3,4-tetrahydroquinoline (**1a**) with D<sub>2</sub>O using various commercially available silver salts as the catalyst. To our delight, 94% deuterium incorporation was achieved in the *ortho*- and *para*-positions by using 10 mol% AgOTf in CDCl<sub>3</sub> at 90 °C (Table 1, entry 1). Other silver salts such as Ag<sub>2</sub>CO<sub>3</sub>, Ag<sub>3</sub>PO<sub>4</sub>, AgBF<sub>4</sub>, AgOAc and Ag<sub>2</sub>O were also tested as catalysts, but gave low deuterium incorporation (entries 2–6). AgOTf showed higher activity probably because of the slow release of TfOH in the reaction.<sup>9a</sup> Control experiment suggests that AgOTf is necessary in this reaction (Table 1, entry 7). We then tested various solvents for this deuteration, and found that THF and 1,4-dioxane can also give good results, but DCE, CH<sub>3</sub>CN afforded a slightly low deuterium incorporation (entries 8–11). The reduction of the D<sub>2</sub>O amount from 20 to 5 equiv. led to a decrease in deuterium incorporation from 94% to 62% (Table 1, entry 12). When the reaction temperature was decreased to 60 °C, the efficiency of deuterium incorporation dramatically decreased, only giving 58% deuterium incorporation in the *ortho*- and *para*-positions (entry 13). In addition, under standard reaction conditions, other Lewis acids such as Cu(OTf)<sub>2</sub>, Zn(OTf)<sub>2</sub>, ZnCl<sub>2</sub>, FeCl<sub>3</sub>, and La(OTf)<sub>3</sub> could also catalyze the H/D exchange, but giving a low deuterium incorporation, especially in the *para*-position.<sup>10,11</sup>

With the optimized catalytic system in hand, we evaluated the scope and limitations of this selective H/D exchange reaction. We firstly examined the deuteration of various electronic-

rich arenes, and the results are listed in Table 2. We were pleased to find out that highly selective H/D exchanges with good to excellent degrees of deuteration were achieved. A variety of substituted 1,2,3,4-tetrahydroquinolines were smoothly converted to the deuterated isotopologues with high levels of deuterium incorporation (**2a–2f**). The bromide and dimethylphenylsilyl substituents could be well tolerated in this catalytic system. The deuteration of indoline derivatives as well as *N*-methyl aniline derivatives could be achieved with good to excellent deuterium incorporation in the *ortho*- and *para*-positions (**2g–2l**). The 9,10-dihydroacridine **1m** was also deuterated to afford **2m** in 88% yield with excellent deuterium incorporation. Moreover, other electron-rich aromatic compounds such as 1,3,5-trimethoxybenzene (**1n**) and multi-substituted anisole (**1o**) were also suitable substrates for the selective deuteration affording **2n** and **2o** with good deuterium incorporation. The conversion of *N,N*-disubstituted aniline derivatives such as *N,N*-dimethylaniline under the standard conditions only led to quite poor D-incorporation (<20% D incorporation).

Subsequently, this catalytic system was applied to the deuteration of indole andazole derivatives. The deuteration of these compounds is of great interest and importance, as they

**Table 1** Optimization of conditions for the silver-catalyzed deuteration of **1a**<sup>a</sup>

Entry	[Ag]	Solvent	Deuterium incorporation (D <sup>1</sup> , D <sup>2</sup> ) <sup>b</sup>
1	AgOTf	CDCl <sub>3</sub>	94%, 94%
2	Ag <sub>2</sub> CO <sub>3</sub>	CDCl <sub>3</sub>	11%, 8%
3	Ag <sub>3</sub> PO <sub>4</sub>	CDCl <sub>3</sub>	21%, 23%
4	AgBF <sub>4</sub>	CDCl <sub>3</sub>	91%, 58%
5	AgOAc	CDCl <sub>3</sub>	21%, 10%
6	Ag <sub>2</sub> O	CDCl <sub>3</sub>	13%, 10%
7	—	CDCl <sub>3</sub>	<5%, <5%
8	AgOTf	DCE	74%, 81%
9	AgOTf	THF	94%, 93%
10	AgOTf	1,2-Dioxane	90%, 90%
11	AgOTf	CH <sub>3</sub> CN	77%, 91%
12 <sup>c</sup>	AgOTf	CDCl <sub>3</sub>	62%, 62%
13 <sup>d</sup>	AgOTf	CDCl <sub>3</sub>	58%, 58%

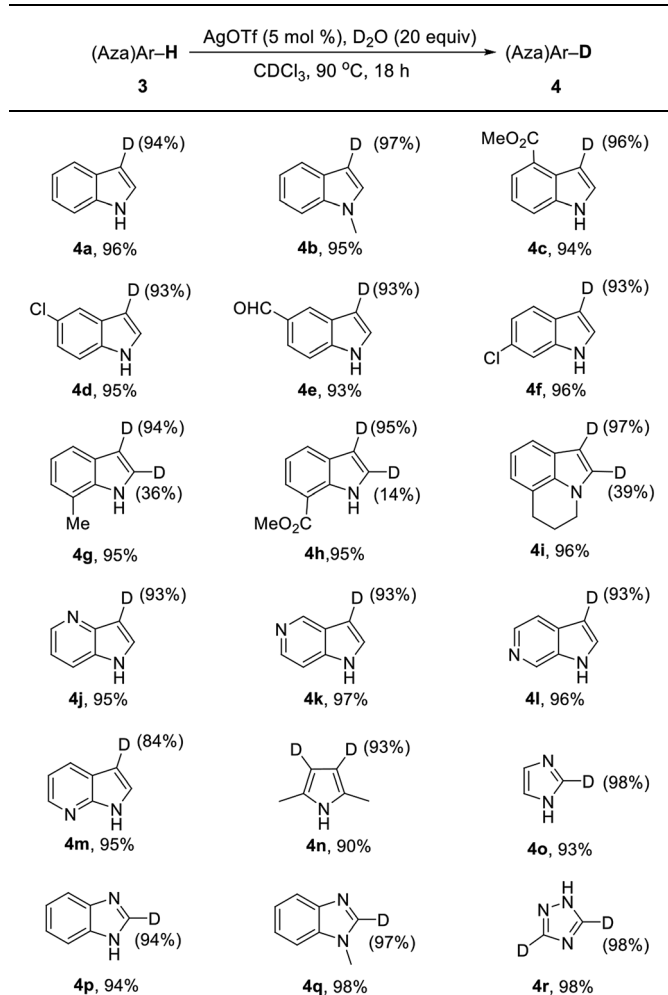
<sup>a</sup> Reaction conditions: **1a** (0.5 mmol), [Ag] (0.025 mmol), D<sub>2</sub>O (10 mmol), solvent (1.0 mL), 90 °C for 18 h. <sup>b</sup> Deuterium incorporation was determined by <sup>1</sup>H NMR. <sup>c</sup> D<sub>2</sub>O (2.5 mmol). <sup>d</sup> At 60 °C.

**Table 2** Silver-catalyzed selective deuteration of various electron-rich arenes<sup>a</sup>

(Het)Ar-H <b>1</b>	AgOTf (5 mol %), D <sub>2</sub> O (20 equiv) CDCl <sub>3</sub> , 90 °C, 18 h	(Het)Ar-D <b>2</b>
<b>2a</b> , 99%		(94%) D, (94%) D
<b>2b</b> , 96%		(84%) D, (84%) D
<b>2c</b> , 94%		(90%) D, (82%) D
<b>2d</b> , 94%		(86%) D, (86%) D
<b>2e</b> , 95%		(87%) D, (87%) D
<b>2f</b> , 95%		(86%) D, (86%) D
<b>2g</b> , 98%		(86%) D, (93%) D
<b>2h</b> , 98%		(90%) D, (91%) D
<b>2i</b> , 97%		(87%) D, (91%) D
<b>2j</b> , 95%		(92%) D, (92%) D
<b>2k</b> , 98%		(83%) D, (87%) D
<b>2l</b> , 94%		(91%) D, D (91%), D (91%)
<b>2m</b> , 88%		D (99%), D (92%)
<b>2n</b> , 99% <sup>b</sup>		D (85%), D (85%), D (85%)
<b>2o</b> , 96% <sup>b</sup>		(83%) D, D (91%), D (91%)

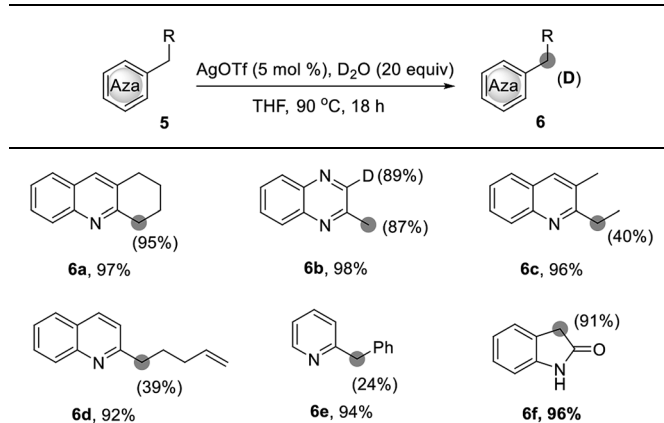
<sup>a</sup> Reaction conditions: **1** (0.5 mmol), AgOTf (0.025 mmol), D<sub>2</sub>O (10 mmol), CDCl<sub>3</sub> (1.0 mL), 90 °C for 18 h. Isolated yield are given. <sup>b</sup> 1,4-dioxane (1.0 mL) was used.



Table 3 Silver-catalyzed selective deuteration of various azaarenes<sup>a</sup>

<sup>a</sup> Reaction conditions: **3** (0.5 mmol), AgOTf (0.025 mmol), D<sub>2</sub>O (10 mmol), CDCl<sub>3</sub> (1.0 mL), 90 °C for 18 h. Isolated yield are given.

are frequently observed in many pharmaceuticals and biologically active molecules.<sup>12</sup> As shown in Table 3, a range of indoles with either electron-rich or electron-poor substituents were smoothly deuterated at C3 positions to afford deuterium-labelled products in excellent yields with good to excellent deuterium incorporation (**4a–4m**). Notably, functional groups such as chloride, ester, and aldehyde were well tolerated with this catalytic system. The 2,5-dimethyl pyrrole (**3n**) was also suitable substrate to afford **4n** with 93% deuterium incorporation in the C3 and C4 positions. Remarkably, electron-deficient azaarenes such as imidazoles and benzimidazole were also readily deuterated at C2 positions with high levels of deuterium incorporation. 1-Methyl benzimidazole (**3q**) could be also employed in this catalytic system, affording **4q** with 97% deuterium incorporation. Also, 1,2,4-triazole could be smoothly deuterated at C3 and C5 positions with excellent deuterium incorporation. Unfortunately, the conversion of benzoxazole

Table 4 Silver-catalyzed  $\alpha$ -deuteration of 2-alkyl azaarenes<sup>a</sup>

<sup>a</sup> Reaction conditions: **5** (0.5 mmol), AgOTf (0.025 mmol), D<sub>2</sub>O (10 mmol), THF (1.0 mL), 90 °C for 18 h. Isolated yield are given.

and benzothiazole under the standard conditions could not lead to D-incorporation.

Furthermore, by using this silver catalytic system, we also successfully achieved the regioselective deuteration at the  $\alpha$ -positions of 2-alkyl azaarenes. As shown in Table 4, the deuteration of 1,2,3,4-tetrahydroacridine gave the deuterated product **6a** efficiently with 95% deuterium incorporation under the current reaction conditions. When the 2-methylquinoline was employed, both methyl group and C3 position were readily deuterated with high deuterium incorporation. In addition, the  $\alpha$ -positions of alkyl-substituted quinolines **5c**, **5d** and 2-benzylpyridine **5e** could be deuterated, giving the corresponding products in good yields, albeit with 24–40% deuterium incorporation. Also,  $\alpha$ -deuteration of oxindole **5f** gave deuterated product **6f** in 96% yield and 91% deuterium incorporation.

## Conclusions

In summary, we have developed an efficient silver-catalyzed regioselective deuteration of (hetero)arenes and  $\alpha$ -deuteration of 2-alkyl azaarenes using the simple D<sub>2</sub>O as the deuterating reagent. The reaction proceeds under neutral mild conditions in high yields with a good to excellent degree of deuterium incorporation. Electron-rich arenes and heteroarenes, such as 1,2,3,4-tetrahydroquinolines, indoline derivatives, *N*-methyl anilines, 1,3,5-trimethoxybenzene and indoles, were all deuterated with high deuterium incorporation. The protocol was also applied to the deuteration of electron-deficient azoles. Moreover, the  $\alpha$ -position deuteration of 2-alkyl azaarenes was also achieved under mild neutral conditions.

## Conflicts of interest

There are no conflicts to declare.



## Acknowledgements

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