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Silver-catalyzed regioselective deuteration of (hetero)arenes and α -deuteration of 2-alkyl azaarenes†

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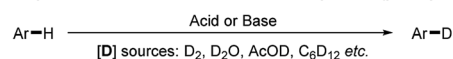
A simple silver-catalyzed regioselective deuteration of (hetero)arenes and α -deuteration of 2-alkyl azaarenes has been described. This strategy provides an efficient and practical avenue to access various deuterated electron-rich arenes, azaarenes and α -deuterated 2-alkyl azaarenes with good to excellent deuterium incorporation utilizing D₂O 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,¹ tools for elucidation of reaction mechanisms,² metabolic or pharmacokinetic probes,³ and as biologically active compounds and pharmaceuticals.⁴ 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,⁵ 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 compounds⁶ (Scheme 1a) and transition metal catalyzed site-selective H/D exchange reactions⁷ (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

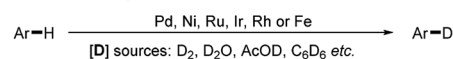
the growing demand for deuterium-labelled compounds in synthetic chemistry and pharmaceutical industry.

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.⁸ However, despite considerable progress, silver-catalyzed selective H/D exchange reaction has remained much less explored to date.⁹ Quite recently, Huang reported an efficient Ag₂CO₃-catalyzed H/D exchange of five-membered heteroarenes using D₂O as deuterium source at ambient temperature, but external base such as 1 equiv. of K₂CO₃ and a phosphine ligand were still needed.^{9b} We here developed a practical and selective silver-catalyzed deuteration of (hetero)arenes and α -deuteration of 2-alkyl azaarenes utilizing D₂O 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

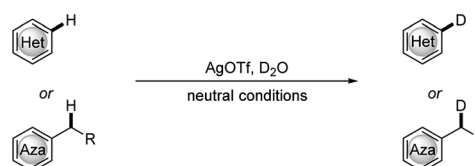
a) Acid/base promoted deuteration of aromatic compounds (pH-dependence)



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



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



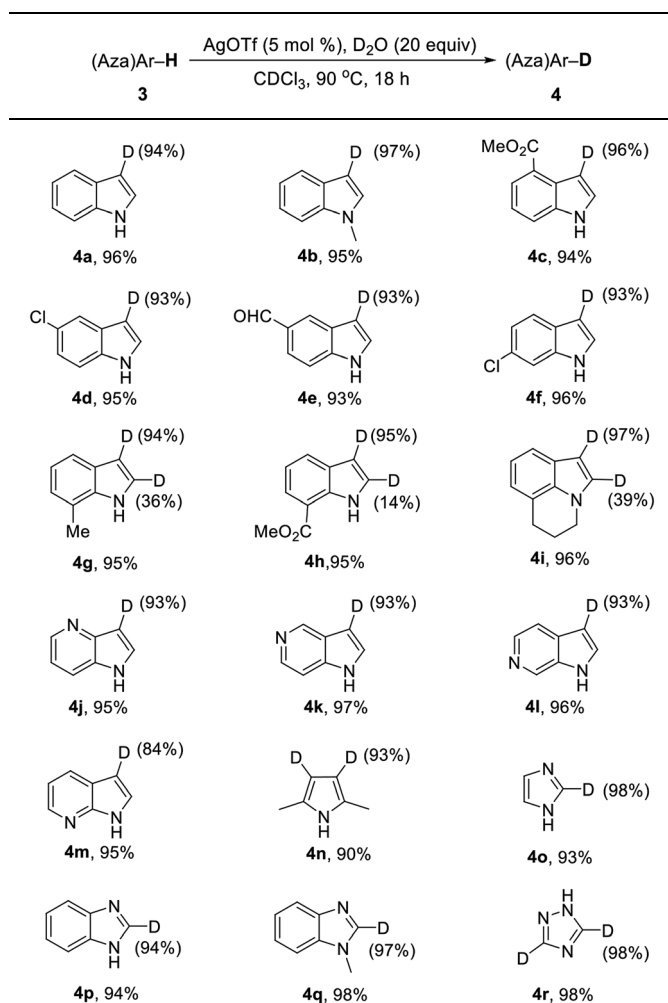
Scheme 1 Selective H/D exchange reactions.

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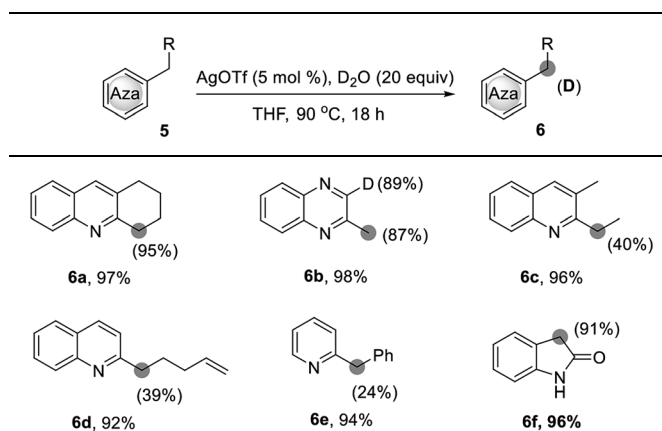
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Table 3 Silver-catalyzed selective deuteration of various azaarenes^a

^a Reaction conditions: **3** (0.5 mmol), AgOTf (0.025 mmol), D₂O (10 mmol), CDCl₃ (1.0 mL), 90 °C for 18 h. Isolated yield are given.

are frequently observed in many pharmaceuticals and biologically active molecules.¹² 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 α -deuteration of 2-alkyl azaarenes^a

^a Reaction conditions: **5** (0.5 mmol), AgOTf (0.025 mmol), D₂O (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 α -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-methyl-quinoline was employed, both methyl group and C3 position were readily deuterated with high deuterium incorporation. In addition, the α -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, α -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 α -deuteration of 2-alkyl azaarenes using the simple D₂O 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 α -position deuteration of 2-alkyl azaarenes was also achieved under mild neutral conditions.

Conflicts of interest

There are no conflicts to declare.



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