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Ag(I)-Mediated hydrogen isotope exchange of mono-fluorinated (hetero)arenes†

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An efficient approach to install deuterium into mono-fluorinated (hetero)arenes by a Ag_2CO_3 /Sphos-mediated HIE protocol with D_2O as the deuterium source has been disclosed. This method showed a specific site selectivity of deuteration at the α -position of the fluorine atom, which is complementary to the existing transition metal-catalyzed HIE process.

Deuterated compounds are widely utilized as internal standards in mass spectrometry,¹ for the mechanistic study in chemical and biological processes,² and for the investigation of the structure and dynamics in soft matter through neutron scattering.³ Due to the higher bond dissociation energy of the C–D bond *versus* C–H bond, deuteration is commonly used to alter the therapeutic profile and metabolic fate of drugs, while retaining their original biochemical potency and selectivity.⁴ Moreover, deuterated compounds have also found applications in the production of advanced functional materials for organic light-emitting devices and organic/polymer solar cells.⁵

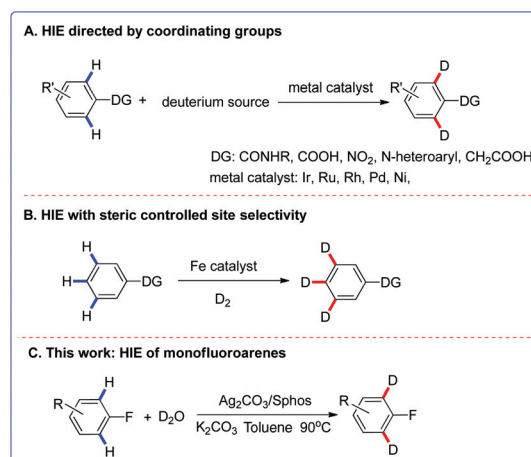
As one of the most efficient and straightforward strategies for the synthesis of deuterated organic compounds, direct hydrogen isotope exchange (HIE) has recently attracted great attention (Scheme 1).⁶ A common strategy to facilitate H/D exchange processes and to control site selectivity focusses on the use of directing groups containing N or O atoms to coordinate with a metal catalyst.^{7,8} However, the site-selective H/D exchange protocol for simple (hetero)arenes lacking a coordinating group remains challenging.^{9,10} In 2016, great advances were made by the Chirik group using an iron complex as a catalyst, affording deuterated arenes with special sterically controlled site selectivity.¹¹ Following this work, the same group developed an H/D exchange protocol with a nickel complex as a catalyst, selectively occurring at the α -position of simple pyri-

dine derivatives.¹² Despite significant advances being made, further expanding the substrate scope of simple (hetero)arenes for the HIE protocol is highly desirable.

Fluorinated arenes are one of the most prominent structural motifs in drug candidates, occurring in 32 of 200 best-selling drugs in 2018.¹³ Although the deuteration of fluoroarenes could be a useful approach to prepare deuterium-labeled active pharmaceutical ingredients for absorption, distribution, metabolism and toxicity studies, a preparative method for deuteration of mono-fluorinated (hetero)arenes *via* H/D exchange has rarely been explored.¹⁴ In addition, the cross-coupling reaction by C–H activation of mono-fluorinated (hetero)arenes also suffered from low efficiency and narrow substrate scope, even when using monofluoroarenes as solvent.¹⁵ In our laboratory, we recently developed a new H/D exchange protocol with a combination of Ag_2CO_3 and a phosphine ligand as a catalyst and demonstrated that the adoption of carbonate salts instead of carboxylic salts as additives played a key role in achieving H/D exchange of five-membered heteroarenes at room temperature.¹⁶ Herein, we report an efficient H/D exchange protocol

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Scheme 1 Deuteration *via* HIE.

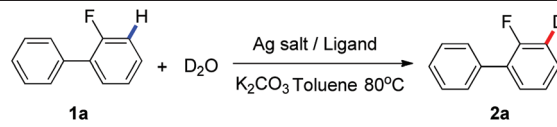
for the incorporation of deuterium into a wide range of mono-fluorinated (hetero)arenes with D₂O as the deuterium source.

Our study began with using a combination of Ag₂CO₃/JohnPhos, which has been found to be a robust catalytic system for the H/D exchange protocol of five-membered heteroarenes. We found that products with only 5% deuterium incorporation formed even at elevated temperature, which suggested that the H/D exchange process is very slow under these conditions. We then screened the solvents for the reaction and found that toluene is the best, affording 15% deuterium incorporation (see Table S1† for details). Concentration played an important role in the H/D exchange process, as a higher level of deuterium incorporation at 43% was achieved using a smaller volume of toluene (Table 1, entry 1). The choice of the phosphine ligand is crucial, and a high level of deuterium incorporation at 91% was observed with SPhos as the ligand (Table 1, entries 1–10). The examination of additives showed that K₂CO₃ is the best for the H/D exchange process, affording 91% deuterium incorporation (see Table S2† for details). These results also suggested that K₂CO₃ can promote the H/D exchange process. The atom% of deuterium incorporation can be further increased by conducting the reaction at a slightly higher temperature (Table 1, entries 11 and 12). Various silver salts other than Ag₂CO₃ were examined and found to be less efficient, giving the product with lower deuterium incorporation (Table 1, entries 13–16). In addition, no deuterium incorporation was observed without adding a silver

salt, which suggested that a silver salt is essential for this reaction (Table 1, entry 17). The attempt to reduce the amount of Ag₂CO₃ and Sphos was unsuccessful. When the reaction was conducted with 20 mol% of Ag₂CO₃ and Sphos, the atom% of deuterium incorporation was 36% at 80 °C and 72% at 120 °C (Table 1, entries 18 and 19). This result suggested that the silver salt may serve as the catalyst for this reaction. Therefore, the optimal conditions were established with Ag₂CO₃/Sphos as the catalyst and K₂CO₃ as an additive in toluene at 90 °C.

With the optimal reaction conditions in hand, we set out to explore the generality of this method with respect to fluorinated arenes. As shown in Table 2, we found that a wide range of functional groups including nitrile, ketone, alkoxy, nitro, amide, alkynyl, alkyl, and halogen (Br) groups are compatible with the reaction conditions. The monofluoroarenes with substituents at different positions are also examined. The monofluoroarenes with *ortho*-substitution are wide substrates for HIE, affording the desired products **2a–2d** with moderate-to-high atom% deuterium incorporation. Interestingly, we found deuterium-labeling also occurring at the α position of the alkoxy group of product **2d**, suggesting that the alkoxy group may also promote the H/D exchange process. The monofluoroarenes with *para*-substituents enabled the H/D exchange process to occur at both the α positions of the fluorine atom,

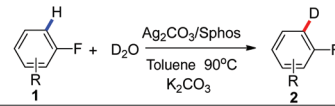
Table 1 Reaction optimization



Entry ^a	Ag salt	Ligand	D incorporation ^b
1	Ag ₂ CO ₃	JohnPhos	43%
2	Ag ₂ CO ₃	<i>t</i> -Bu ₃ P	26%
3	Ag ₂ CO ₃	<i>t</i> -Bu ₂ (2-MeC ₆ H ₄)P	26%
4	Ag ₂ CO ₃	(<i>o</i> -MePh) ₃ P	6%
5	Ag ₂ CO ₃	Ph ₃ P	5%
6	Ag ₂ CO ₃	(<i>p</i> -OMePh) ₃ P	15%
7	Ag ₂ CO ₃	(<i>o</i> -MePh) ₃ P	6%
8	Ag ₂ CO ₃	MePhos	90%
9	Ag ₂ CO ₃	DavePhos	82%
10	Ag ₂ CO ₃	SPhos	91%
11 ^c	Ag ₂ CO ₃	SPhos	96%
12 ^d	Ag ₂ CO ₃	SPhos	96%
13	Ag ₂ O	SPhos	65%
14	AgBr	SPhos	1%
15	AgCl	SPhos	1%
16	AgOAc	SPhos	1%
17	None	SPhos	0%
18 ^e	Ag ₂ CO ₃	SPhos	36%
19 ^f	Ag ₂ CO ₃	SPhos	72%

^aThe reaction was conducted on 0.3 mmol of **1a**, 6 mmol of D₂O, 50 mol% of Ag salt, 50 mol% of ligand and 0.3 mmol of K₂CO₃ in toluene at 80 °C. ^bDetermined by GC-MS. ^c90 °C. ^d100 °C. ^e20 mol% of Ag₂CO₃ and 20 mol% of SPhos. ^f20 mol% of Ag₂CO₃ and 20 mol% of SPhos 120 °C.

Table 2 Deuteration of monofluoroarenes^a



2a : 85% [90%]	2b : 40% ^b [89%]	2c : 95% [89%]
2d : 90% [74%] [28%] D	2e : 40% ^b [93%]	2f : 92% [95%]
2g : 92% [85%]	2h : 87% [80%]	2i : 93% [73%]
2j : 95% [89%]	2k : 90% [86%] [38%]	2l : 80% [72%] [25%]
2m : 86% [90%]	2n : 95% [85%]	2o : 90% [65%]
		2p : 88% [91%]

^aThe reaction was conducted with compound **1** (1 mmol), D₂O (10 mmol), Ag₂CO₃ (0.5 mmol), Sphos (0.5 mmol) and K₂CO₃ (1 mmol) in 1 mL of toluene at 90 °C for 12 hours; deuterium incorporation was estimated using ¹H NMR spectra; isolated yield. ^bVolatile liquid.

affording products with 73% to 95% deuterium incorporation (2e–2j). The H/D exchange process with *meta*-substituted monofluoroarenes showed site selectivity, possibly due to the steric effect of phenyl groups (2k–2l). The use of 4,4'-difluorodiphenyl and 4,4'-difluoro-benzophenone as starting materials led to the H/D exchange of four C–H bonds, providing 65% and 91% deuterium incorporation, respectively. In all cases, deuterium preferred to install at the *ortho*-position to the C–F bond, which is possibly due to the greater acidity of the C–H bond *ortho* to the C–F bond.¹⁷ It is worth noting that the deuteration of 4,4'-difluoro-benzophenone may lead to novel ultra-long organic phosphorescent materials, since it is an important intermediate for organic phosphorescent materials.¹⁸

Since nitrogen-containing heteroarenes are common structural motifs in functional materials and bioactive compounds, we next turned our attention to examine the H/D exchange process with monofluorinated nitrogen-containing heteroarenes as starting materials. As shown in Table 3, pyridine derivatives with fluorine substituted at different positions are wide substrates for the Ag₂CO₃-mediated H/D exchange reaction, and excellent atom% deuterium incorporation is commonly observed with the exception of product 4c. The great difference in atom% deuterium incorporation observed between products 4a (94%) and 4c (55%) suggested that a steric effect may lead to the loss of efficiency in the H/D exchange process. When a fluorine atom was installed at the position *meta* to the pyridine nitrogen (compound 4d–4g), the H/D exchange process preferentially occurred at the *para*-position over the *ortho*-positions, possibly due to the difference in the pK_a of the C–H bond at these positions.^{17b} The low yields

of compounds 4d and 4g may be attributed to the volatile properties and low boiling points of 4d and 4g. It is worth noting that this Ag₂CO₃-mediated HIE protocol showed orthogonal site selectivity to other metal catalysts, preferentially occurring at the 3, 4, and 5 positions of pyridine derivatives.¹² Furthermore, we found that monofluoroquinoline and monofluoropyrimidine derivatives are wide substrates (4h–4j), providing a high level of deuterium incorporation even for the substrate with an amine group directly attached at the pyrimidine ring. With the exception of the electron-deficient arenes, the H/D exchange of electron-rich 2-chloro-5-fluorobenzo[*d*]thiazole was also tested and it afforded a product with 90% deuterium incorporation, which further expands the scope of this reaction.

To further demonstrate the specific site selectivity of this Ag₂CO₃-mediated H/D exchange protocol, we conducted the reaction with 2-(4-fluorophenyl)pyridine as the starting material. As shown in Scheme 2, the H/D exchange occurred at different positions with Ag₂CO₃/Sphos and a Ru complex as the catalyst, respectively.¹⁹ Based on this result, we prepared deuterium-labeled 2-(2,4-difluorophenyl)pyridine, which is a key motif for a famous blue light-emitting material named Firpic.²⁰ Deuterium-labeling of Firpic is expected to prolong the corresponding device's lifetime.²¹

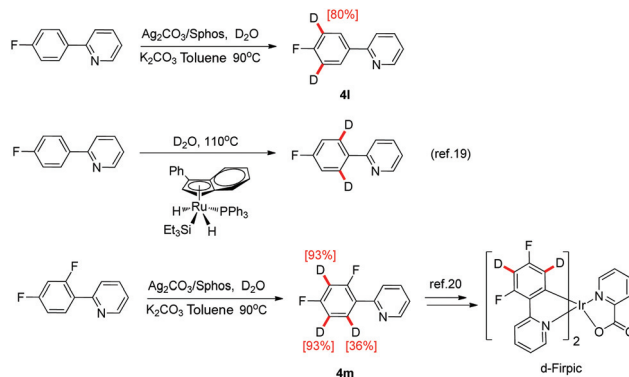
After establishing the utility of this Ag₂CO₃-mediated H/D exchange protocol on a wide range of monofluorinated (hetero)arenes, we attempted to apply this method to the late-stage deuterium-labelling of drug molecules. Although it is challenging to introduce deuterium at the C(sp²)–H bond in the antipsychotic drug iloperidone by traditional metal-catalyzed HIE protocols, the Ag₂CO₃-mediated H/D exchange on 5a afforded 6a labeled at the fluorinated phenyl ring and methyl group with a high level of deuterium incorporation (Scheme 3).

We then investigated the mechanism. A mechanism involving free radicals should be discounted, because the radical inhibitor TEMPO has no negative effect on the reaction (see the ESI† for details). Based on our experimental evidence and previous reports,^{16a,22} we proposed a plausible mechanism pathway. First, the silver carbonate-mediated concerted meta-

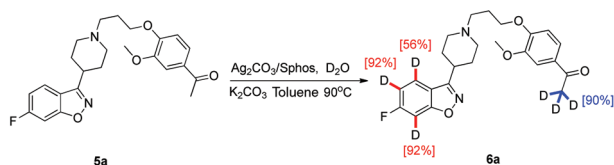
Table 3 Deuteration of fluorinated nitrogen-containing heteroarenes^a

Product	Atom% D	Yield (%)
4a	[94%]	90%
4b	[88%]	80%
4c	[55%]	96%
4d	[97%]	53%
4e	[86%]	86%
4f	[95%]	80%
4g	[96%]	50%
4h	[28%]	89%
4i	[84%]	86%
4j	[92%]	93%
4k	[92%]	80%

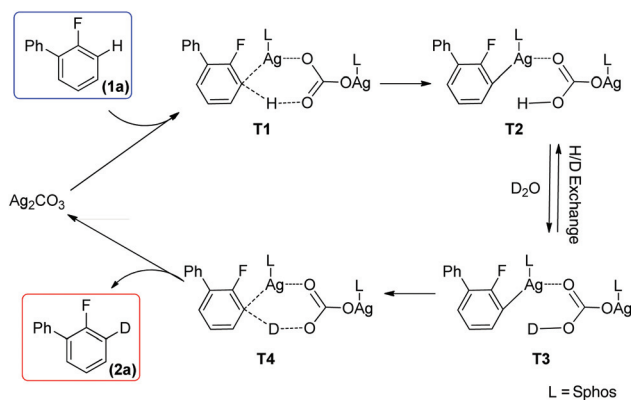
^a The reaction was conducted with compound 3 (1 mmol), D₂O (10 mmol), Ag₂CO₃ (0.5 mmol), Sphos (0.5 mmol) and K₂CO₃ (1 mmol) in 1 mL of toluene at 90 °C for 12 hours; deuterium incorporation was estimated using ¹H NMR spectra; isolated yield.



Scheme 2 Site selectivity of Ag₂CO₃-mediated HIE.



Scheme 3 Deuteration of iloperidone.



Scheme 4 Plausible mechanism for Ag-mediated HIE.

lation deprotonation step leads to the C–H bond activation of fluorinated arenes. Then, the H/D exchange may occur between T2 and heavy water to form T3, followed by deuterium incorporation and regeneration of silver carbonate (Scheme 4).

In summary, a general approach to install deuterium into mono-fluorinated (hetero)arenes by H/D exchange is disclosed. A wide range of fluorinated (hetero)arenes are found to be compatible with this transformation, which widely expanded the substrate scope of the H/D exchange protocol. In addition, we applied this method for the deuterium-labelling of selected commercial drugs and advanced functional materials. Further work is underway in our laboratory to explore the scope of this Ag_2CO_3 -mediated HIE process and the isotope effect of deuterated functional materials. These studies will be reported in due course.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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