

Multideuteration of Nitroaromatics by Silver-Catalyzed Hydrogen-Isotope Exchange

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Abstract

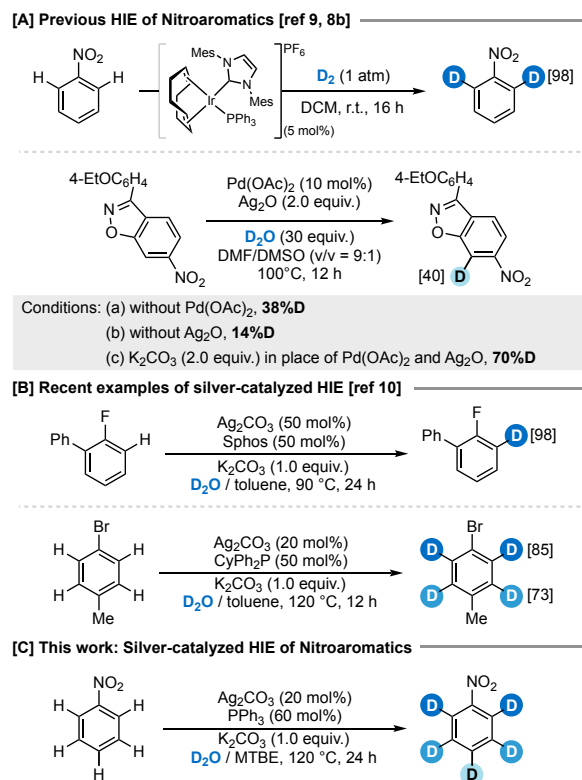
A silver-catalyzed deuteration of nitroaromatics had been achieved employing D₂O as deuterium source. Distinct from the well-established directing group guided hydrogen-isotope exchange, the protocol showed an interesting deuteration pattern, where considerable deuterium accumulation was observed around the aromatic ring. Control experiment indicated the deuteration was initiated by a silver-promoted C-H activation, and a tentative two-stage deuteration mechanism involving aryl-silver species was proposed to explain the deuteration on *meta*- and *para*-sites.

Introduction

With the increasing demands of deuterium labelling in pharmaceutical and material science,¹ the development of novel strategies had been urged to provide deuterated compounds with various structures and divergent labelling sites. Among the methods established,² hydrogen-isotope exchange (HIE) had attracted considerable attention as an ideal and intuitive route, which *in-situ* replacing the protium with deuterium. With the recent booming of C-H activation,³ the HIE had been boosted by transition metal catalysis,⁴ especially with the assistance of directing groups such as carbonyl, pyridyl, and amide.^{2c} In contrast, the selective deuteration of compounds without strong directing groups remain challenging due to lack of anchoring position.

Nitroaromatics, with a strong electro-withdrawing NO₂ group, had acted as an important chemical source,⁵ and had been subjected by the modern cross-couplings as a leaving group in the past years.⁶ However, the substrate suggests an unfavored feature for prevailing electrophilic C-H activation: 1) the low electro-density retards the C-H activation, and 2) the weak coordinating ability makes the pre-activation intermediate unstable. Despite the recent achievements of their C-H functionalization,⁷ only rare cases had been reported for the direct deuteration of nitroaromatics.⁸ Besides its first disclosure from Kerr using electron-rich Iridium complex (Scheme 1A),⁹ a recent mechanistic study indicated the potential of higher deuteration activity of AgO than Pd(OAc)₂.^{8b} The subsequent test with K₂CO₃ suggested the exchange may be conducted via a S_NAr pathway. This interesting finding encouraged us to hypothesize the electron-rich silver-complex could facilitate the HIE of electro-deficient nitroaromatics. Noticeably, similar strategy of silver-catalysis had been proven by Zhang in the selective deuteration of electro-deficient substrates such as fluoro-, bromo-, and heteroaromatics (Scheme 1B),¹⁰ whose catalytic species was elucidated by Hartwig recently.¹¹ Herein, we wish to unveil our recent progress in the HIE of nitroaromatics, as one of our long term goal to build-up the arsenal for deuteration.

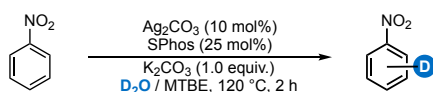
Scheme 1. The deuteration of nitroaromatic compounds and the recent development of silver-mediated deuteration.



Our investigation was commenced with nitrobenzene (**1**) as model substrate, and the initial attempt showed an encouraging deuterium incorporation of 0.54D using the combination of Ag₂CO₃/SPhos/K₂CO₃ (Figure 1A, entry 1). After the confirmation of the necessity of the catalyst, ligand, and base (Figure 1A, entries 2-3), the performance of different ligands was evaluated firstly. Biaryl phosphines failed to yield any better results. Meanwhile, the simple phosphines ligands such as PPh₃, CyPPh₂, and PCy₃ pushed the deuterium accumulation over 1.5D within 2 hours (Figure 1A, entries 5-7). A survey of pre-catalyst showed Ag₂CO₃ as the optimal choice, while other silver, copper, or gold salts didn't render any better results (Figure 1A, entries 8-11). Although the exchange was expected to conduct at *ortho*-sites, deuterium incorporation over 2.0D was observed when prolonging the reaction time (Figure S1). The subsequent NMR analysis showed the *meta*-positions also suffered the deuteration, which indicates an underlying relationship with Zhang's deuteration of bromoaromatics.^{10c} Meanwhile, the accumulation of aniline and phosphine oxide in this long time exchange also led us to question the stability of the catalytic system.

After the confirmation of non-catalytic activity of triphenylphosphine oxide (Figure 1A, entry 12), an accelerated experiment was conducted under 140 °C to evaluate the influence between ligand oxidation and deuteration rate. As shown in Figure 1B, the most electron-rich PCy₃ rendered a rapid deuterium accumulation in its first hours' exchange. But the following exchange was stagnated due to the ligand consuming. Similar deceleration was also observed in the cases of PCyPh₂ and PPh₃, where the former also rendered an extremely poor recovery less than 30%. Thus, further optimization was conducted based on PPh₃ as ligand, and rendered an optimal condition for nitrobenzene with a deuterium distribution of 98%D, 31%D, and 19%D at *ortho*-, *meta*-, and *para*-positions, respectively.¹³¹⁴

[A] Catalytic System optimization ^a



no	deviation from initial condition	%D ^b
1	none	0.54
2	without silver and/or ligand	0
3	without K ₂ CO ₃	0.83
4	biaryl phosphines (DavePhos, JohnPhos, MePhos)	< 0.60
5	PCy ₃ (30 mol%)	1.61 (2.61) ^c
6	PCyPh ₂ (30 mol%)	1.60 (2.08) ^c
7	PPh ₃ (30 mol%)	1.55 (3.44) ^c
8	Ag ₂ O (10 mol%) and PPh ₃ (30 mol%)	1.22
9	AgOAc (20 mol%) and PPh ₃ (30 mol%)	0.54
10	AgTFA (20 mol%) and PPh ₃ (30 mol%)	0.13
11	CuCl, CuI, or Ph ₃ PAuCl (20 mol%) and PPh ₃ (30 mol%)	0
12	O=PPh ₃ (30 mol%)	0

[B] Relationship of ligand oxidation and deuteration progression ^d

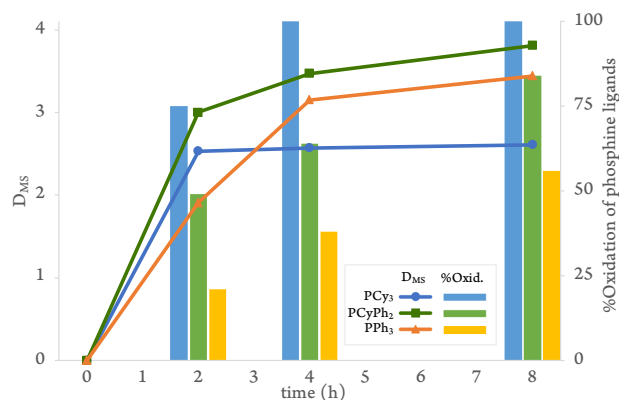
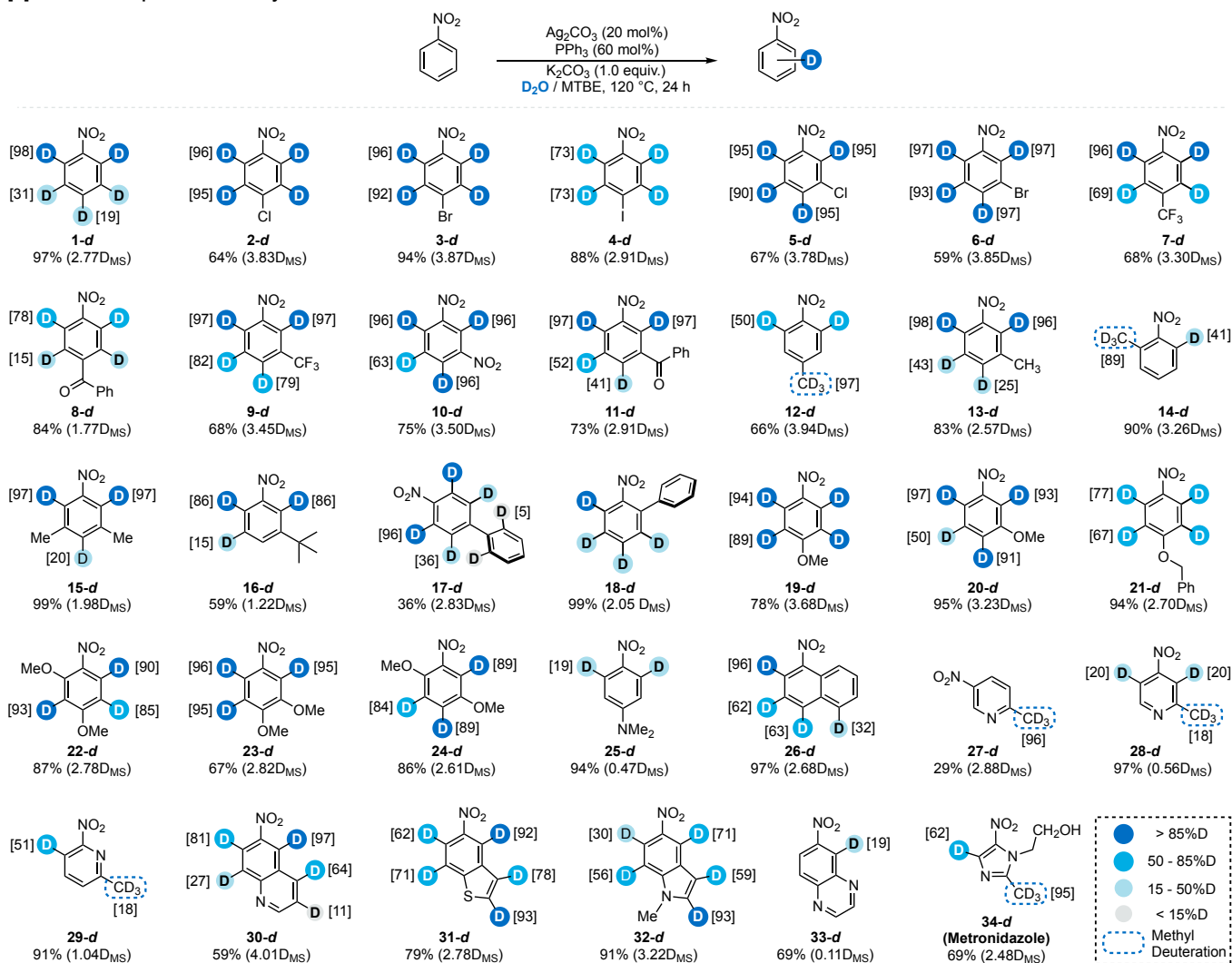


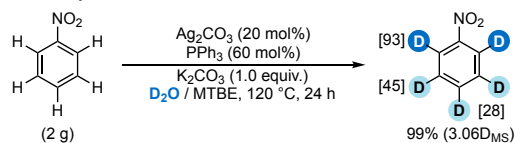
Figure 1. (A) Evaluation of HIE Condition for Nitrobenzene, and (B) relationship of ligand oxidation and deuteration progression. ^a The reaction was conducted with **1a** (2.0 mmol) under specified conditions; ^b %D determined by GC-MS; ^c Accelerating reaction conducted under 140 °C. See Table S2 for detailed experiment data; ^d See Table S5 for detailed experiment data.

With optimal condition established, the performance of the deuteration system was examined on various nitroaromatics (Figure 2A). The halogen containing substrates was tested firstly (**2 – 6**), which had been reported to be deuterated efficiently under the similar system.^{10c} As expected, both chloro- and bromo-substituted nitrobenzene rendered product with high deuterium incorporation, where nitro group showed a slight higher inductive effect in deuteration. Other substrates bearing electron-withdrawing groups were also subjected (**7 – 11**), which rendered a confusing division with different substitution pattern. When the functional group located at *meta*-position, all the compounds rendered acceptable results with moderate to excellent deuterium incorporation (**7 – 9**). However, the *para*-substituted ones showed a dramatic decrease in *meta*-deuteration. 1,4-Dinitrobenzene even failed in deuteration. Interestingly, similar result was observed in methyl substituted ones (**12 – 14**). For the *ortho*- and *para*-methyl nitrobenzenes, only a moderate *ortho*-deuteration was observed on the phenyl ring, meanwhile the methyl was deuterated completely (**12 and 13**).¹⁵ In contrast, a satisfying deuterium incorporation was found with the substrates with *meta*-methyl substitution (**14 and 15**), which left methyl untouched. Interference from steric hindrance was observed on 3-*tert*-butyl and 3-phenyl nitrobenzenes. Substrates bearing electro-donating groups were also tested (**19 – 24**), where ether substitution rendered good to excellent results. A poor result of 19%D was obtained with 4-dimethylamino substitution, whose enhanced electro density may retard the initial C-H bond insertion. Subsequent testing of 1-nitronaphthalene (**26**) showed an interesting deuteration sequence long the 2 to 5 positions. We also tested

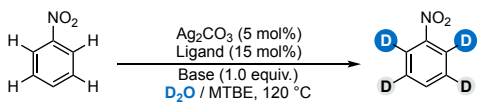
[A] Substrate Scope of Silver-Catalyzed Deuteration of Nitroaromatics.^{a,b,c}



[B] Gram-scale experiment



[C] *Ortho*-selective deuteration of nitrobenzene



entry	Ligand	Base	t (hr)	%D _{ortho}	%D _{meta}
1	PPh ₃	K ₂ CO ₃	8	94	10
2	PPh ₃	KHCO ₃	8	70.5	2.5
3	PPh ₃	KHCO ₃	24	91.5	7.0
4	PCy ₃ HBF ₄	K ₂ CO ₃	8	37	0
5	PCy ₃ HBF ₄	K ₂ CO ₃	24	94	5

[D] Synthetic application

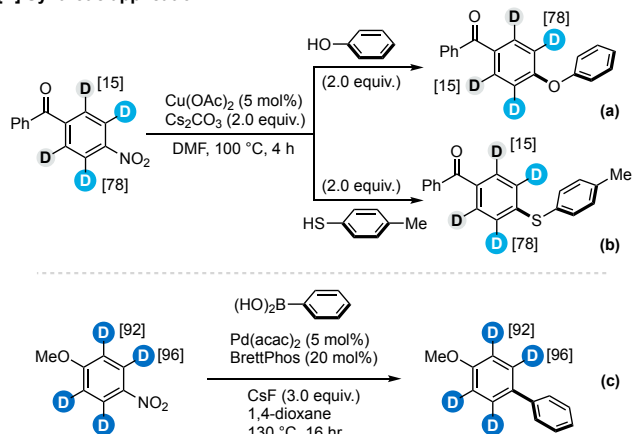


Figure 2. Substrate scope, gram-scale preparation, ortho-selective exchange, and synthetic application of deuterated nitroaromatics. ^aReaction condition (unless noted otherwise): nitroaromatics (1 mmol), Ag₂CO₃ (20 mol%), PPh₃ (60 mol%), K₂CO₃ (1.0 equiv.), MTBE (0.2 mL), and D₂O (1.0 mL), 120 °C, 24 hr. ^bYield for volatile compounds was calculated by HPLC with external standard. ^cDeuterium incorporation is detected by GCMS (denoted in parenthesis as D_{MS}) and deuterium distribution (denoted in square brackets at the specific site) was

calculated by the peak integrity of $^1\text{H-NMR}$ based on GC-MS result, for symmetric positions only one %D shown; ^dYield after column separation.

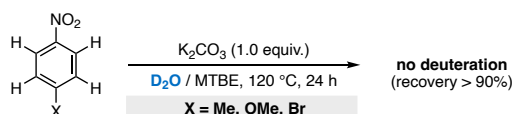
a series of nitro-heterocycles. For the case of methyl pyridines (**27 – 29**), nitro located at 5-position failed to render any expected *ortho*-deuteration result, while the others only afford a middle level %D. Quinoline, benzothiophene, and *N*-methyl indole (**30 – 32**), with nitro located at the *para*-site of heteroatoms, showed moderate deuterium incorporation around the aromatic system. However, 6-nitro quinoxaline (**33**) failed to render an acceptable result, which may be due to the increased electro-density from 4-nitrogen. Metronidazole (**34**), an antibiotic and anti-protozoal reagent, also tolerated the condition, incorporating the deuterium on both *ortho* and methyl positions.

Further examination of the utility of this Ag-catalyzed HIE was commenced with a gram-scale experiment. As expected, the reaction rendered a quantitative recovery after distillation, with a slightly elevated deuterium incorporation (Figure 2B). We also found the rate of *meta*-deuteration could be suppressed by introducing acid salts, where $\text{PCy}_3\cdot\text{HBF}_4$ rendered the highest selectivity of 94:5 (Figure 2C). Subsequently, chemical transformation of deuterated nitroaromatics was conducted to show its potential as a deuterio-building block for further functionalization. As expected, cross-coupling reaction with nitrobenzenes, including C-O, C-S, and C-C bond couplings,¹⁶ didn't affect the deuterium distribution (Figure 2D), all the transformation left labelled sites intact. A Bartori indole synthesis was also performed with *ortho*-deuterated nitrobenzene,¹⁷ which also kept the %D after the treatment of Grignard reagent (see supporting information for details).

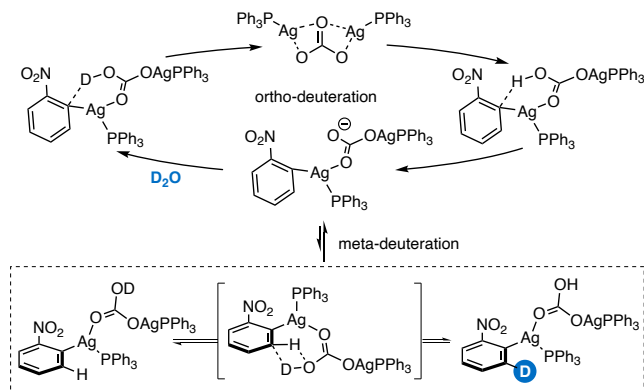
Despite the above results showed a promising application of the reaction, the unexpected deuterium distribution still triggered our curiosity. Especially the failing of deuteration on *para*- and *ortho*-methyl nitrobenzenes (**12** and **14**). To wipe out the potential base-promoted deuteration with substituted nitrobenzenes, a background test subjecting 4-methyl nitrobenzene with K_2CO_3 was conducted (Scheme 3A), suggesting the exchange was occurred under the presence of silver (Scheme 3A). Meanwhile, 4-bromo- and 4-methoxy- substrates also led to the similar results. Thus, we postulate the *meta*-deuteration was conducted after the initial C-H activation, where the aryl-silver species enhanced the aromatic ring's electron density, especially at the *meta*-sites. Based on this postulation and previous mechanistic works,^{10a, 11} a two-stage mechanism was proposed tentatively to explain the phenomenon (Scheme 3B): The initial rapid C-H activation is conducted by an electro-enriched Ag-species (**I**) via a $\text{S}_{\text{N}}\text{Ar}$ process on *ortho*-position. The intermediate (**II**) lead to an enhancement of electro-density on *meta*-position, as well as other positions, facilitating the H/D exchange under the framework of $\text{S}_{\text{E}}\text{Ar}$ pathway. The second-stage deuteration may conduct at a much slower rate, and is influenced by the aryl-silver species' stability, which lead to a little lower deuterium incorporation at *meta*-position. This also explained the suppression from acid salts to the *meta*-deuteration (Figure 3C). To support the postulation, a preliminary theoretical analysis of HOMO indicated an enhanced nucleophilicity at *meta*- and *para*-positions for this aryl-silver species (Figure 3C). Furthermore, an additional analysis was conducted with bromo and fluorobenzene, where the former showed a similar nucleophilicity enhancement at *meta*-site. Meanwhile no elevation was found in fluorobenzene, which also matched the experimental results well.^{10b, 10c}

Scheme 3. Control Experiments and Proposed Mechanism

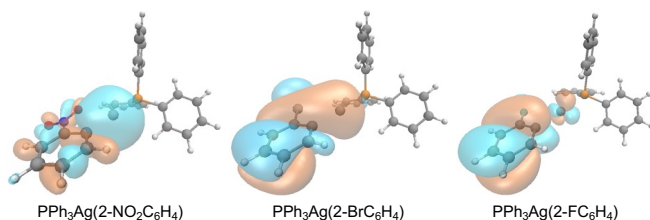
[A] Control experiments



[B] Proposed Two-Cyclic Mechanism



[C] Electro-density analysis of post C-H activation species



Conclusion

In summary, a deuteration protocol was developed for nitroaromatics via a silver-catalyzed hydrogen-isotope exchange employing D_2O as deuterium source. Preliminary substrate examination rendered a series nitroaromatics with good to excellent deuterium incorporation around the aromatic rings. The deuterated products were proved as reliable deuterium modules for synthesis without disturbing the deuterium distribution. A two-stage deuteration process was proposed to explain the unexpected H/D exchange on *meta* and *para*-sites, where the process may conduct after the initial formation of aryl-silver species at *ortho*-position. Further mechanistic study is now under investigation.

ACKNOWLEDGMENTS

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13. The optimal condition Ag₂CO₃ (20 mol%), PPh₃ (45 mol%), K₂CO₃ (0.51.0 equiv.), D₂O (25 equiv.), and MTBE (0.2 M), see supporting information for detailed optimization data
14. Catalytic system with 5 mol% and 10 mol% Ag₂CO₃ loading could also rendered satisfactory results for the deuteration of nitrobenzene as 2.50DMS and 2.83DMS within 24 hours, respectively. However, those condition showed poor efficiency in preliminary substrate scope test as shown in Figure S2.
15. Control experiment without silver and ligand failed to render deuteration on methyl.

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