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H-D exchange in deuterated trifluoroacetic acid via ligand-directed NHC-palladium catalysis: a powerful method for deuteration of aromatic ketones, amides, and amino acids

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Abstract

A method has been developed for one-step *ortho*-selective ligand-directed H-D exchange, accompanied in some cases by concurrent acid-catalyzed electrophilic deuteration. This method is effective for deuteration of aromatic substrates ranging from ketones to amides and amino acids, including compounds of biological and pharmaceutical interest such as acetaminophen and edaravone. Use of a palladium catalyst featuring an NHC ligand is critical for the observed reactivity. Experimental evidence strongly suggests that palladium facilitates C-H activation of the aromatic substrates, a mechanism seldom observed under strongly acidic conditions. 2015 Elsevier Ltd. All rights reserved.

Graphical Abstract

Keywords

H-D exchange; Palladium; NHC; CF₃COOD

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Supplementary Material

Supplementary material, including ¹H NMR spectral data, is available online in PDF format.

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Introduction

Development of efficient, practical methods for H-D exchange has accelerated as a result of the rapidly increasing commercial importance of deuterated compounds. Of particular interest are deuterated pharmaceuticals, the commercial value of which is expected to eventually exceed 1 billion USD.¹ One deuterated drug, the tetrabenazine derivative SD-809, has shown promising results during phase 3 clinical trials for chorea associated with Huntington's disease.² A number of catalytic processes have been investigated to produce these valuable deuterium-labeled compounds, including metal-free conditions as well as both homogeneous and heterogeneous metallic catalysts.³ Of the homogenous transition metal-catalyzed methods for H-D exchange of pharmaceutically relevant compounds, most have focused on the use of rhodium and iridium⁴ although H-D exchange of other small molecules by homogenous ruthenium,⁵ palladium^{5a,6} and platinum^{5a,6b,7} species has also been reported. These reactions are frequently conducted in deuterated acidic media such as acetic acid-d₄ or trifluoroacetic acid-d₁ (CF₃COOD). However, recent studies have called into question whether certain metal-catalyzed H-D exchange reactions in acidic solvents proceed through C-H activation or electrophilic aromatic substitution mechanisms; in CF₃COOD, the latter mechanism has been suggested to predominate.^{5a,8}

Ligand-directed C-H activation by palladium is a versatile method for highly selective functionalization of otherwise unreactive C-H bonds. Numerous challenging transformations have been carried out using this approach, including alkylation, olefination, alkynylation, arylation, and amidation reactions, among others.⁹ While several different mechanistic pathways are possible depending on the specific reaction, generally the substrate undergoes cyclopalladation with the ligated palladium catalyst to generate the reactive intermediate.^{9a} Weakly-coordinating ligands such as ketones and carboxylic acids have recently emerged as promising directing groups for palladium-catalyzed organic synthesis. Because palladacycles formed using weakly-coordinating directing groups are generally less thermodynamically stable than their tightly-bound counterparts, they are thus more reactive towards functionalization.^{9c}

A few reports of ligand-directed H-D exchange using rhodium¹⁰ and ruthenium^{5b-c} catalysts have been published, although most studies employ iridium complexes.¹¹ Recently, a report of ligand-directed palladium-catalyzed *ortho*-selective H-D exchange of benzoic acids and phenylacetic acids using weak coordination has been published.^{6a} The H-D exchange of benzene and other hydrocarbons in D₂O with NHC-amidate palladium catalyst **1** has been previously investigated.^{6c} The use of CF₃COOD as a solvent, catalyst, and source of deuterium label for anilines and acetanilides has also been established.¹² Herein is reported an H-D exchange methodology that utilizes both of these strategies simultaneously to effect the *ortho*-selective H-D exchange of aromatic amides, ketones, and amino acids. In several cases, this ligand-directed C-H activation process occurs in conjunction with electrophilic H-D exchange by CF₃COOD, allowing for complete H-D exchange of pharmaceutically relevant compounds such as acetaminophen. This distinguished reactivity provides a complimentary strategy for previously inaccessible deuterated substrates.

Results and Discussion

Our previously reported electrophilic H-D exchange method using CF₃COOD without any additional metal catalyst was highly effective for aromatic amides and amines.¹² However, this method was ineffective for more electron-poor substrates such as acetophenone and its derivatives, and the use of a homogeneous palladium catalyst in conjunction with CF₃COOD was considered to improve the extent of deuteration.

Ketones have been employed as directing groups for numerous different metal-catalyzed transformations, including *ortho*-selective H-D exchange with iridium¹¹ and ruthenium.^{5b} To determine the viability of a palladium-catalyzed H-D exchange method using a ketone as a directing group, 2-acetonaphthone was subjected to reaction with CF₃COOD in the presence of several different palladium(II) complexes and additives (Table 1).

In the absence of any palladium catalyst, no significant H-D exchange occurred on the aromatic rings although extensive H-D exchange was observed on the acetyl group (entry 1). Most common palladium salts showed negligible improvement over the control experiment (entries 2 – 5), although Pd(TFA)₂ exhibited minor activity (entry 6). While these known catalysts favored regioselective H-D exchange of H₁, Pd-NHC catalyst **1** (10 mol%) effected an improved rate of deuteration at H₂ preferentially (entry 7). Activation of the palladium salts with AgTFA was then investigated. When activated Pd(PPh₃)₂Cl₂ (generated via addition of two equivalents of AgTFA) and AgTFA alone were used as catalysts, reactivity was unchanged relative to the control experiment (entries 8 – 9).

However, the use of catalyst **1** with AgTFA (10 mol%) resulted in a significant increase in the extent of H-D exchange observed, far superior to any of the other palladium salts tested. Substitution of deuterium was selective, occurring predominantly at one position (H₂), *ortho* to the ketone (entry 10). Adding AgOTf in place of AgTFA resulted in reduced H-D exchange as well as partial degradation of the substrate (entry 11).

In the presence of Pd-NHC catalyst **1**, various reaction conditions were then investigated (Table 2). Additional AgTFA resulted in no improvement (entry 1 vs entry 2), and reducing the catalyst loading lowered the extent of H-D exchange somewhat (entry 3). At lower temperatures, very low amounts of deuterium incorporation were observed (entry 4). Increasing or decreasing the volume of CF₃COOD gave approximately a 10% reduction in deuterium incorporation (entries 5 – 6). Little or no H-D exchange was observed when deuterated acetic acid or methanol was used in place of CF₃COOD as a solvent (entries 7 – 8). Longer reaction times did not result in a proportional increase in deuterium incorporation (entry 9). It was concluded that the original conditions did not require further optimization.

The substrate scope of this method was evaluated by testing several different aromatic ketones in the presence of catalyst **1** and AgTFA (Scheme 1). The method was less effective for unsubstituted acetophenone **2** compared to 2-acetonaphthone **6**, resulting in 25% total *ortho*-selective deuterium incorporation. The aliphatic protons adjacent to the carbonyl (acetyl protons) were mostly exchanged with deuterium (>90%); this H-D exchange occurred with all substrates tested independent of palladium catalyst. Similarly, deuterium incorporation in 4'-methoxyacetophenone **3** was marginally improved by the palladium

catalyst. Interestingly, while the Pd-NHC catalyst efficiently deuterated highly activated ketone **4** more effectively than CF₃COOD, the nitro-substituted ketone **5** was unresponsive to the developed conditions, suggesting a strong dependence on the electronic properties of the aromatic ring. As explained above, 2-acetonaphthone **6** exhibited far superior reactivity and selectivity under the palladium-catalyzed conditions. Other bicyclic ketones such as **7** and **8** were moderately deuterated with a high degree of *ortho* selectivity. However, when the ketone was distal to the aromatic ring such as in dibenzyl ketone **9**, almost no *ortho* incorporation of deuterium was observed.

Encouraged by these promising results with ketones, we turned our attention to acetanilide derivatives (Scheme 2). Acetanilides have been extensively utilized as directing groups for palladium-catalyzed C-H functionalization reactions and have also been employed to direct H-D exchange reactions with rhodium,^{10c} iridium,¹¹ and ruthenium.^{5c} The palladium-catalyzed *ortho*-selective H-D exchange of acetanilides was envisaged proceeding in a similar fashion to ketones under identical conditions. Our previous work¹² identified acetanilides as substrates well-suited for electrophilic H-D exchange in CF₃COOD, so care was taken to identify any improvement in *ortho*-selective deuterium incorporation by catalyst **1**.

Electron-rich and electron-neutral acetanilides **10–13** were deuterated efficiently under the described conditions, although electron-poor acetanilide **14** had significantly lower deuterium incorporation. Notably, one-step, nearly complete ring deuteration of pharmaceutically-relevant acetaminophen **13** was achieved, which was a significant improvement over existing literature methods which required multiple inefficient synthetic steps¹³ or only partially deuterated the aromatic ring.^{10c,11e,14} As with ketone substrate **9**, distal amide substrate **15** was ineffective at promoting H-D exchange. Conversely, pyrazolone-substituted substrate **16**, the pharmaceutically-relevant compound edaravone, was selectively *ortho*-deuterated in good yield in the presence of catalyst. Benzamide **17** was somewhat reactive towards the palladium catalyst but was deuterated much less efficiently than the acetanilides. In summary, the palladium-catalyzed conditions led to a high degree of H-D exchange selectively *ortho* to the amide group, a significant improvement over the previously developed CF₃COOD conditions.

The H-D exchange of aromatic amino acids using this method was also considered. Various methods for ring deuteration of phenylalanine and tyrosine derivatives, generally employing acid catalysis, have been reported in the literature.^{7f–g,15} Palladium-catalyzed *ortho* functionalization of aromatic amino acids such as phenylalanine and tyrosine and their derivatives has been conducted¹⁶ but typically uses methyl esters¹⁷ or sulfonamides¹⁸ to efficiently direct C-H activation. It was found that simple unmodified α-phenylglycine **18** and phenylalanine **19** were deuterated selectively at the *ortho* positions by the developed catalytic method (Scheme 3). Previously, aromatic deuterium incorporation *ortho* to the side chain of phenylalanine was achieved by selective protonation of ring-perdeuterated tyrosine followed by reduction to phenylalanine,^{15c} an inefficient and deuterium-uneconomical strategy. However, palladium-catalyzed *ortho* deuteration was not as effective for tyrosine **20**, and electrophilic H-D exchange by CF₃COOD was predominant. Varying amounts of deuterium incorporation were observed at the stereocenters, and thus some racemization of

the amino acids may have occurred. Interestingly, neither phenylacetic acid **21** nor benzylamine **22** showed selectivity towards H-D exchange by the palladium catalyst, suggesting that efficient ligand direction does not occur in the absence of the amine or carboxylic acid functional groups.

Based on the experimental evidence collected, a catalytic cycle was envisioned (Scheme 4) involving coordination of the palladium-NHC complex **1** to the substrate of interest, followed by C-H activation of an accessible aromatic proton. This process may involve formation of an agostic complex with assistance from coordinated trifluoroacetate, as evidenced in several computational studies.¹⁹ Subsequent deuteration would furnish the deuterated substrate and regenerate the catalyst. This proposed mechanism is conceptually very similar to that suggested by Yu et al. in the palladium-catalyzed H-D exchange of phenylacetic acids and other arenes.^{6a} The active intermediate for such a C-H activation reaction would presumably be a cyclopalladated aryl-Pd(II) complex; however, this proposed intermediate could not be isolated. Acid-catalyzed H-D exchange by CF₃COOD, following a simple electrophilic aromatic substitution pathway, would be concomitant with several substrates.

While evidence suggests metal-catalyzed H-D exchange reactions of arenes in strong acids such as CF₃COOD, especially with additives such as AgTFA, are in many cases predominantly electrophilic,^{5a,8} a Lewis-acid type H-D exchange mechanism under the described conditions is unlikely for several reasons. First, Lewis-acid catalyzed H-D exchange is typically restricted to nonpolar arenes^{3a} without functional groups that the Lewis acid could coordinate to preferentially. Moreover, simple palladium salts were not nearly as effective catalytically as the NHC-palladium complex **1**, which exhibits increased thermal stability and electron density on palladium due to strong σ donation from the NHC ligand. This complex has previously been utilized for H-D exchange reactions under neutral conditions.^{6c} In this case, the role of the AgTFA is thus to abstract chloride from palladium to generate an open coordination site, not to increase the Lewis acidity of the metal center. Additionally, the high degree of *ortho* selectivity observed for H-D exchange of ketones, without comparable *meta* or *para* reactivity, further suggests a C-H activation mechanism. Finally, when AlCl₃ was utilized in place of palladium with 2-acetonaphthone **6**, no improvement over simple acid-catalyzed conditions were seen, both with and without stoichiometric AgTFA additive.

Conclusion

Using a palladium-NHC catalyst in deuterated trifluoroacetic acid, one-step ligand-directed *ortho*-selective H-D exchange of aromatic ketones, amides, and amino acids has been conducted. The Pd-NHC complex tested showed distinguished reactivity compared to other palladium salts, which were ineffective deuteration catalysts. In general, acetanilides were more reactive than ketones, and a strong correlation of reactivity with the electronic properties of the aromatic ring was observed. Direct *ortho* deuteration of amino acids was possible without prior functionalization at nitrogen or oxygen. Experimental data supports the intermediacy of an aryl-palladium species generated by C-H activation of the coordinated substrate rather than Lewis acid-type catalysis. With highly activated substrates,

substantial concurrent acid-catalyzed electrophilic H-D exchange also occurred, resulting in nearly complete ring deuteration of several acetanilides, including pharmaceutically-relevant acetaminophen. *Ortho*-selective aromatic functionalization with other electrophiles besides deuterium cation may be possible using a variant of this method. Further work will explore this possibility and investigate synthetic modification of the catalyst scaffold and development of additional NHC ligands to improve catalytic activity and selectivity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
NHC-amidate palladium catalyst **1**.

Scheme 1.

H-D exchange of aromatic ketones with CF₃COOD (condition **a**) and CF₃COOD with catalyst **1** and AgTFA (condition **b**). The bracketed numbers adjacent to each aromatic position represent percent deuterium incorporation at that position (combined in the case of a symmetrical structure.) Isolated yields are given in parentheses.

Scheme 2.

H-D exchange of aromatic amides and their derivatives with CF₃COOD (condition **a**) and CF₃COOD with catalyst **1** and AgTFA (condition **b**). Results **10a–14a** are from our previous work¹² using identical conditions and are shown for comparison purposes. No deuterium incorporation was observed at the amide substituents after workup. The bracketed numbers adjacent to each aromatic position represent percent deuterium incorporation at that position (combined in the case of a symmetrical structure.) Isolated yields are given in parentheses. ^aKeto-enol tautomerism prevents accurate determination of deuterium incorporation at the pyrazolone methylene position.

Scheme 3.

H-D exchange of amino acids and derivatives with CF₃COOD (condition **a**) and CF₃COOD with catalyst **1** and AgTFA (condition **b**). ^aThe bracketed numbers adjacent to each aromatic position represent percent deuterium incorporation at that position (combined in the case of a symmetrical structure.) Isolated yields are given in parentheses.

Scheme 4.

Plausible mechanism of palladium-catalyzed H-D exchange.

Table 1Effect of palladium salts and AgTFA additive on H-D exchange.^a

Entry	Catalyst	Additive	% D (H ₁)	% D (H ₂)
1	none	-	6	2
2	PdCl ₂	-	6	2
3	Pd(MeCN) ₂ Cl ₂	-	6	2
4	Pd(OAc) ₂	-	7	4
5	Pd(PPh ₃) ₂ Cl ₂	-	5	1
6	Pd(TFA) ₂	-	9	9
7	1	-	6	13
8	Pd(PPh ₃) ₂ Cl ₂	AgTFA ^b	6	1
9	none	AgTFA	6	1
10	1	AgTFA	11	86
11	1	AgOTf	_c	_c

^a H-D exchange of other aromatic positions has been omitted for clarity.^b 0.04 mmol AgTFA was added.^c Significant degradation of the substrate was observed.

Table 2Effect of reaction conditions on H-D exchange.^a

Entry	1 (mol%)	AgTFA (mol%)	solvent	% D
1	10	10	CF ₃ COOD	86
2	10	20	CF ₃ COOD	82
3	5	5	CF ₃ COOD	72
4 ^b	10	10	CF ₃ COOD	9
5 ^c	10	10	CF ₃ COOD	77
6 ^d	10	10	CF ₃ COOD	76
7	10	10	DOAc-d ₃	0
8	10	10	MeOD-d ₃	1
9 ^e	10	10	CF ₃ COOD	85

^a H-D exchange of other aromatic positions has been omitted for clarity.^b Reaction conducted at 60 °C.^c 0.5 mL of CF₃COOD was added.^d 2 mL of CF₃COOD was added.^e Reaction proceeded for 36 h.