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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.

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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 iridium[4] 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-d_4 or trifluoroacetic acid-d_1 (CF_3COOD). 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 CF_3COOD, 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 toward functionalization.[9c]

A few reports of ligand-directed H–D exchange using rhodium[10] 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 D_2O with NHC–amidate palladium catalyst **1** has been previously investigated.[6c] The use of CF_3COOD 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

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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 CF_3COOD, 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

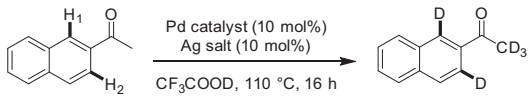
Our previously reported electrophilic H–D exchange method using CF_3COOD without any additional metal catalyst was highly effective for aromatic amides and amines.[12] However, this method was ineffective for more electron-poor substrates such as acetophenone and its derivatives, and the use of a homogeneous palladium catalyst in conjunction with CF_3COOD 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 iridium[11] 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 CF_3COOD 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 H_1, Pd–NHC catalyst **1** (10 mol %) effected an improved rate of deuteration at H_2 preferentially (entry 7). Activation of the palladium salts with AgTFA was then investigated. When activated $Pd(PPh_3)_2Cl_2$ (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 and 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 (H_2), *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) (Fig. 1).

Table 1
Effect 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	$Pd(MeCN)_2Cl_2$	—	6	2
4	$Pd(OAc)_2$	—	7	4
5	$Pd(PPh_3)_2Cl_2$	—	5	1
6	$Pd(TFA)_2$	—	9	9
7	**1**	—	6	13
8	$Pd(PPh_3)_2Cl_2$	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.

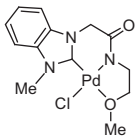


Figure 1. NHC–amidate palladium catalyst **1**.

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 CF_3COOD gave approximately a 10% reduction in deuterium incorporation (entries 5 and 6). Little or no H–D exchange was observed when deuterated acetic acid or methanol was used in place of CF_3COOD as a solvent (entries 7 and 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 CF_3COOD, 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 out 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 work[12] identified acetanilides as substrates well-suited for electrophilic H–D exchange in CF_3COOD, 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 steps[13] 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,

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