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A Protocol for the *Ortho*-Deuteration of Acidic Aromatic Compounds in D_2O Catalyzed by Cationic Rh^{III}

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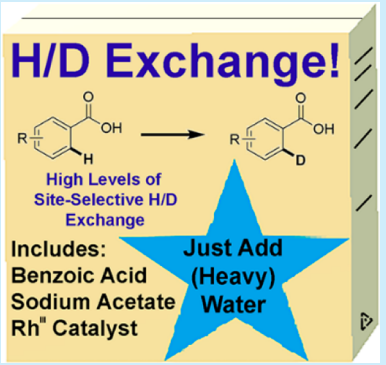
Supporting Information

ABSTRACT: Methods to catalytically introduce deuterium in synthetically useful yields *ortho* to a carboxylic acid directing group on arenes typically requires D_2 or high catalyst loadings, which makes using these approaches cost prohibitive for large-scale synthesis (equipment and reagent costs respectively). Herein, we present a simplified approach using low catalyst loadings of cationic Rh^{III} and D_2O as both deuterium source and solvent and show its application to H/D exchange on various carboxylic acid substrates.



Selective incorporation of deuterium into organic compounds is vital for a variety of applications,[1] including kinetic isotope experiments,[2] internal standards for analytical applications,[3] and labeled probes for studying metabolomics.[4] Exchanging H for D can also lead to modified pharmacological properties.[5] Unsurprisingly, a number of synthetic methods have been developed to replace hydrogen atoms with deuterium. These include stoichiometric directed metalation,[6] per-deuteration of aromatic[7] or aliphatic[8] C−H bonds, and catalytic directed metalation[9] strategies. Most of these methods achieve site-selective H/D exchange (HDE) using either excess D_2[10] or acetic acid-d_4.[11] There are reports that make use of site-selective C−H deuteration of aryl carboxylic acids with D_2O as the deuterium source, typically using Group VIII metals,[12] but these struggle from numerous challenges, including catalyst decomposition,[13] the need for cosolvents,[14] or conversion into a better directing group.[15] The ability to use solely D_2O as solvent and as a deuterium source while using low catalyst loading would lead to a straightforward way to prepare *ortho*-deuterated aromatic carboxylic acids in a more sustainable and straightforward fashion and at larger scale and lower cost with common laboratory equipment.

Much of the work in HDE catalyzed by Group VIII metals has focused on low-valent species, or the free metal halide salts. Based on the precedent of C−H activation of benzoic acids to form new C−C bonds using Rh^{III} catalysts,[16] we set out to determine the optimal conditions for our desired C−H deuteration reaction on 3-(trifluoromethyl)benzoic acid as the model substrate using Rh^{III} precatalysts and determined that the best system involved using 1.0 mol % of the cationic complex $[Rh(cp^*)(MeCN)_3](SbF_6)_2$ with 1.1 equiv of NaOAc as base and ∼200 equiv of D_2O as the solvent. All reactions were performed in triplicate, and the average yield/deuteration was reported. The reaction was run for 24 h at 90 °C, resulting in 98% deuteration at C^6 as determined by ^1H NMR (Table 1, **1**). This also led to 92% deuteration at the C^2 position, suggesting that steric blocking of the 2-position is not as viable an approach as it is in other C−H activation reactions.[17] The catalyst loading could be dropped to only 0.25 mol % without a significant decrease in the level of deuteration at C^6, although deuteration at C^2 became less favorable (**2**), consistent with previous observations.[18] Using $RhCl_3{\cdot}3H_2O$ (**3**) gave poor conversion, probably due to the rate of catalyst decomposition without the stabilizing cp* ligand.[13]

Halide dimers of Rh or Ir[19] cyclopentadienyl-based catalysts were not as effective (**4** and **5**), showing good C^6 deuteration, but reduced HDE at C^2. Ru was completely ineffective (**6** and **7**).[20] Despite precedence in similar reactions using acetic acid-d_4, we found that $Pd(OAc)_2$ was not effective in our system (**8**).[11] Unsurprisingly, no deuteration was observed in the absence of transition-metal catalyst (**9**). Changing the identity of the base also had a detrimental effect (**10**−**12**). We found that the reaction was not complete at shorter reaction times (**13** and **14**), while lowering the temperature led to decreased levels of deuteration (**15** and **16**). Raising the temperature leads to lower levels of HDE (**17**), probably due to catalyst decomposition. Meanwhile, at the lower temperature of 70 °C, the reaction will continue to give slightly higher levels of HDE if left beyond 24 h (**18**), even at lower catalyst loadings (**19**).

Using our optimized conditions, we were able to isolate the model substrate in 93% yield with the previously observed 98%

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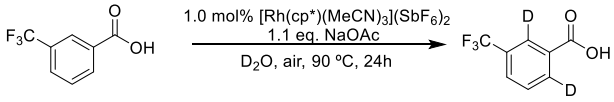
Table 1. Optimization Study of the C−H Deuteration of 3-(Trifluoromethyl)benzoic Acid (0.26 mmol Scale)

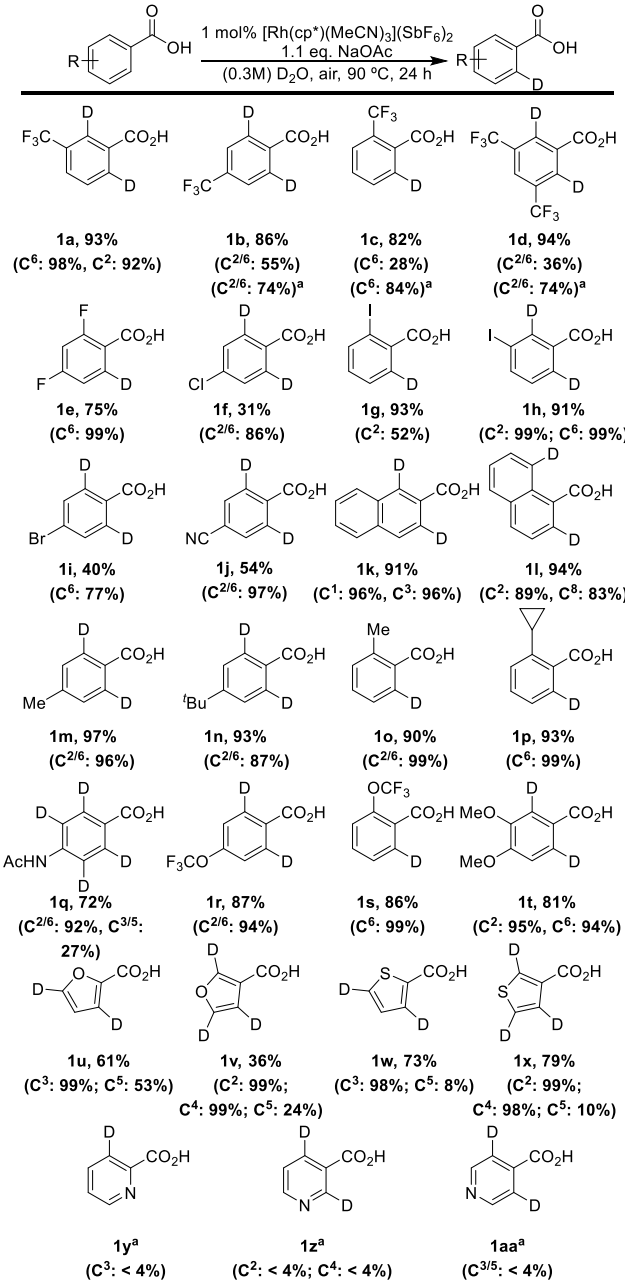


entry	deviation from optimized conditions	C^6C^2 deuteration (%)
1	none	98/92
2	$[Rh(cp^*)](MeCN)_3]SbF_6)_2$ as catalyst (0.25 mol %)	97/67
3	$RhCl_3{\cdot}3H_2O$ as catalyst (1 mol %)	4/6
4	$[Rh(cp^*)Cl_2]_2$ as catalyst (1 mol %)	98/73
5	$[Ir(cp^*)Cl_2]_2$ as catalyst (1 mol %)	98/81
6	$[Ru(cp^*)(cod)Cl]$ as catalyst (1 mol %)	<4/< 4
7	$[Ru(PPh_3)_2Cl_2]$ as catalyst (1 mol %)	<4/< 4
8	$Pd(OAc)_2$ as catalyst (1 mol %)	<4/< 4
9	no catalyst	<4/< 4
10	$NaHCO_3$ as base (1.2 equiv)	65/17
11	Cs_2CO_3 as base (1.2 equiv)	35/9
12	Na_2CO_3 as base (1.2 equiv)	65/17
13	6 h reaction time	97/50
14	12 h reaction time	98/88
15	80 °C reaction temperature	98/90
16	70 °C reaction temperature	95/61
17	100 °C and 0.25 mol % Rh^{III} catalyst loading	93/42
18	70 °C and 48 h reaction time	98/69
19	70 °C, 48 h, and 0.25 mol % Rh^{III} catalyst loading	91/39

deuteration at C^6 and 92% deuteration at C^2 (Scheme 1, **1a**). The percent deuteration was determined using ^1H NMR and, when needed, an internal standard as well as ^2H NMR (to assess nondirected HDE). Notably, shifting the CF_3 group to the *ortho* or *para* position had a profound effect on the level of deuteration (**1b** and **1c**). Gratifyingly, the poor levels of deuteration could be improved simply by increasing the catalyst loading. The same was true for a 3,5-bis-CF_3-substituted substrate (**1d**). Our method was effective on a variety of halogenated substrates containing fluorine (**1e**), chlorine (**1f**), iodine (**1g** and **1h**), and bromine (**1i**) substituents. The *ortho*-iodide gave a small amount of inseparable byproducts, likely due to competitive reaction at the *ortho*-iodide. Even a nitrile substituent could be tolerated in the reaction (**1j**).

The reaction is not limited to simple benzoic acids, and both 2-naphthoic (**1k**) and 1-naphthoic (**1l**) acids gave relatively high levels of deuteration *ortho* to the directing group. In addition to β-C−H activation, substrate **1l** also showed deuteration at the γ-position.[21] Aliphatic substituents on benzoic acid were also tolerated, both at the *para*-position (**1m** and **1n**) as well as at the *ortho*-position (**1o**). In contrast to substrate **1l**, the *o*-CH_3 does not undergo γ-C−H activation. While low-valent metals or radical intermediates will often cleave sensitive cyclopropyls, the Rh^{III} used in this transformation was able to catalyze the transformation while preserving a sensitive *o*-cyclopropyl ring (**1p**). Performing the reaction on 4-acetamidobenzoic acid gave effective *ortho*-deuteration to the carboxylic acid but also lower levels of deuteration *ortho* to the acetamide (**1q**). Trifluoromethoxy substituents (**1r** and **1s**) are tolerated as is a bis-methoxy-substituted ring (**1t**).

Scheme 1. Scope of the C−H Deuteration of *ipso*-Aryl and Heteroaryl Carboxylic Acids (0.30 mmol Scale)



[a]2 mol % of catalyst used. [b]^1H NMR taken directly in D_2O from the crude reaction mixture.

Considering heteroaromatics, 2-furoic acid showed high levels of deuteration at C^3 (**1u**). The electronically biased HDE at C^5 also occurred with 53% exchange.[22] Similarly, 3-furoic acid underwent high levels of exchange at C^2 and C^4, while medium HDE was observed at C^5 (**1v**). In the case of 2-thiophene carboxylic acid, high levels of deuteration were observed at C^3 as expected, but comparatively little at C^5 (**1w**), reflecting the decreased reactivity of thiophenes for C−H activation.[23] Similarly, 3-thiophene carboxylic acid showed high levels of exchange at C^2 and C^4, with very little at C^5 (**1x**). No significant HDE was observed for any of the pyridine carboxylic acids (**1y**−**1aa**).

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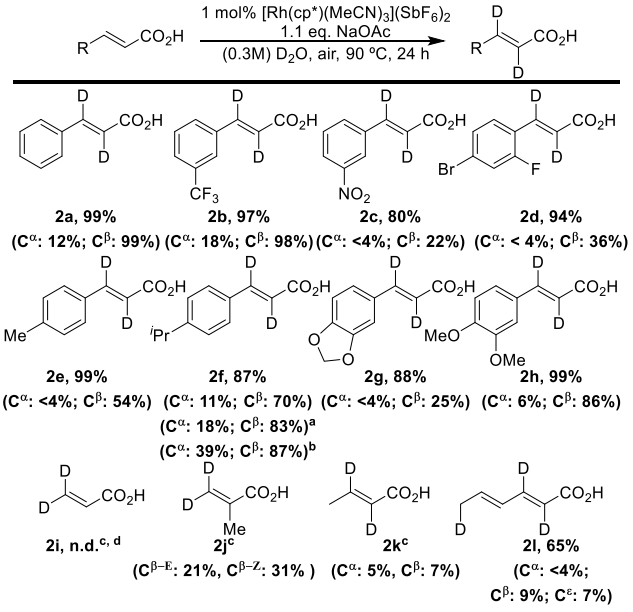
We considered that this method should also be viable for vinylic acids and began studying the reaction on cinnamic acids. Notably, Ru^{II} catalysts are known for promoting HDE on vinylic acids in the presence of either CD_3OD or D_2O.[24] Simple cinnamic acid showed almost complete deuteration at the β-carbon (Scheme 2, **2a**). Low levels of deuteration were

Scheme 2. Scope of the C−H Deuteration of Vinyl Carboxylic Acids (0.30 mmol Scale)



[a]3 mol % of catalyst used. [b]5 mol % of catalyst used. [c]^{1}H NMR taken directly in D_2O from crude reaction mixture. [d]Substrate underwent oligomerization.

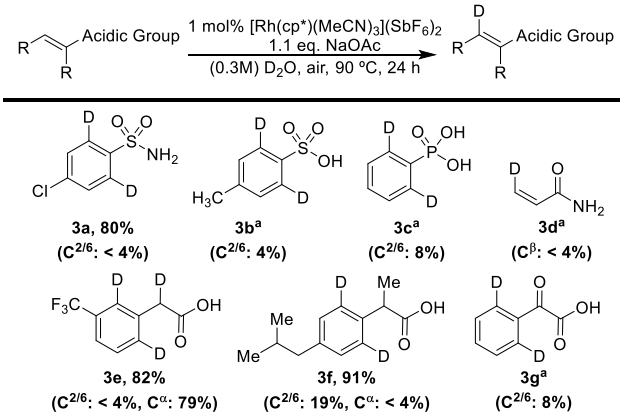
also observed at the α-carbon. Similar results were observed for a 3-(trifluoromethyl)-substituted cinnamic acid (**2b**). Using either a 3-nitro- (**2c**) or 4-bromo-2-fluoro-substituted cinnamic acid (**2d**), low levels of HDE were observed. 4-Methylcinnamic acid was also tested but gave only moderate levels of HDE at C^{β} (**2e**). Surprisingly, use of extra catalyst did not significantly or consistently improve the deuteration for this more poorly soluble example as it did in the cases of **1b**−**1d**. Using a larger ^{i}Pr-substituent led to higher levels of HDE (**2f**), even though it was also insoluble. In this case, increasing the catalyst loading did have a slight impact on improving the deuteration at both C^{β} and C^{α}.

Only poor HDE was observed for a methylene dioxycinnamic acid (**2g**), while a dimethoxy cinnamic acid (**2h**) gave much higher levels of deuteration. To address potential insolubility issues, we looked at addition of both CD_3OD and DMSO-d_6 as cosolvents to the reaction of **2e** and **2a** (see the Supporting Information). Increasing amounts of DMSO-d_6 lowered the amount of HDE, while CD_3OD dramatically increased the HDE on **2e**, but led to a slight decrease for **2a**. Using a 1:1 mixture of CD_3OD/D_2O led to improved HDE for **1c**, **2d**, and **2g**, but not for **2c**, suggesting **2c**'s poor performance in the HDE reaction may be due to factors other than solubility.

Since the method could work on a variety of cinnamic acids, we considered that simpler vinylic acids might also be suitable substrates. However, performing the transformation on acrylic acid gave a complex mixture of possibly deuterated products intermixed with oligomerization products of acrylic acid (**2i**). While methacrylic acid (**2j**) was stable to the conditions, only low levels of HDE were observed. It is unclear whether the enrichment of deuterium at the *trans*-β-hydrogen is due to isomerization of the alkene (installation at the *cis*-position and subsequent isomerization) or undirected C−H activation at the *trans*-β-hydrogen. Poor levels of deuteration were also observed for crotonic (**2k**) and 2,4-hexadienoic (**2l**) acids, suggesting that perhaps the arene in the cinnamic acids is critical for C−H activation.

We next wondered if other acidic functional groups might also participate in the reaction. The reaction with 4-chlorobenzene sulfamide[25] (Scheme 3, entry **3a**) showed no

Scheme 3. Scope of the C−H Deuteration of Various Acidic Substrates (0.30 mmol scale)



[a]^{1}H NMR taken directly in D_2O from crude reaction mixture.

sign of HDE. Even *p*-toluenesulfonic acid gave only trace conversion to the deuterated product (**3b**). Using a phosphonic acid gave slightly improved but still poor levels of deuteration (**3c**). We next tried simple acrylamide (**3d**), and although it did not oligomerize like acrylic acid in our method, no HDE was observed. We next questioned whether or not the carboxylic acid could be moved further away from the arene and still direct C−H activation effectively.[26] When we subjected 3-(trifluoromethyl)phenylacetic acid to the reaction conditions, we observed 79% deuteration, but surprisingly at the α-position (**3e**). This may be a consequence of exchange promoted by the more acidic α-carbon rather than a C−H activation pathway. Meanwhile, only trace HDE was observed on the arene. When we explored the reaction on 2-(4-isobutylphenyl)propanoic acid (ibuprofen, **3f**), either the decreased acidity or increased sterics was able to shut down the α-HDE, leading to slightly increased but still low levels of exchange on the arene. Interestingly, running the reaction in a 1:1 mixture of CD_3OD/D_2O completely shut down the HDE (see the Supporting Information). Considering the increased rigidity of phenylglyoxylic acid, we considered it might be a viable substrate but found similarly poor conversion (**3g**).

We considered that acetylsalicylic acid (aspirin) might make for a nice application of this method on an obvious biologically relevant molecule. When the reaction was attempted under the standard conditions, acetylsalicylic acid was deuterated at the C^6 position almost quantitatively (Scheme 4, **1ab**). However, under the conditions, the acetyl group was completely hydrolyzed. When the reaction temperature was lowered to 80 or 70 °C, lower levels of deuteration were observed, but still

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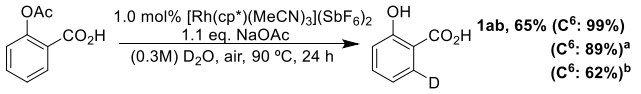
Scheme 4. HDE on the Drug Acetylsalicyclic Acid (0.30 mmol Scale)

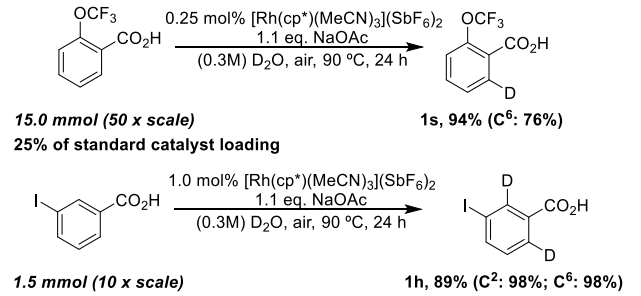


[a]Reaction performed at 80 °C. [b]Reaction performed at 70 °C.

with concomitant loss of the Ac group, suggesting that deuteration from salicylic acid followed by installation of the Ac group would be preferable to prepare aspirin-6-*d*. Interestingly, no exchange was observed at C^3 *ortho* to the phenol.

To demonstrate scalability, we performed the HDE for **1s** but now at 50 times the initial scale (Scheme 5). Due to the cost of the Rh^{III} catalyst, we performed the reaction using a reduced catalyst loading (0.25 mol %), and found that significant deuteration could still be achieved. We also performed the reaction on 3-iodobenzoic acid at 1.5 mmol scale, or 10 times the initial scale. This time we used the same catalyst loading (1 mol %), and found only slight decrease in the level of deuteration.

Scheme 5. Scale-up of the C−H Deuteration of 2-(Trifluoromethoxy)benzoic Acid and 3-Iodobenzoic Acid



We propose for the mechanism (Figure 1) that cationic Rh^{III} first undergoes ligand exchange to install two eq of carboxylate (at least one substrate).[27] An internal concerted metalation-deprotonation step will then lead to C−H activation of the substrate. The protonated carboxylic acid ligand can then undergo HDE with the solvent, followed by deuteration of the Rh−C bond, though direct deuterolysis by solvent is also plausible. Ligand exchange between deutero and protio substrates would then be expected to give turnover.

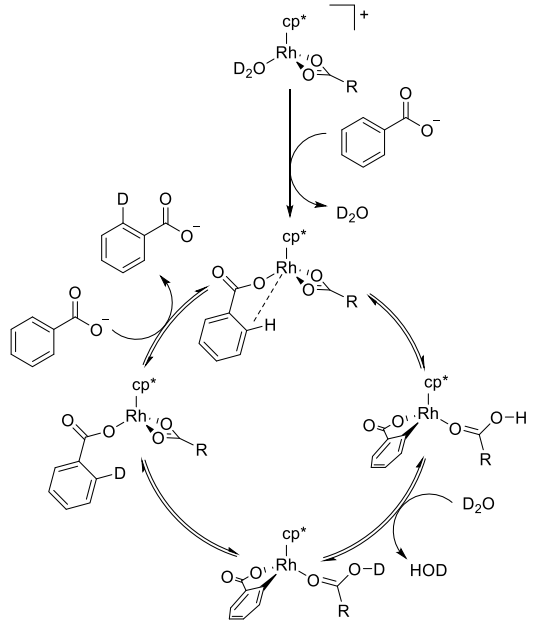


Figure 1. Proposed mechanism for C−H deuteration using Rh^{III}.

In conclusion, we have developed a simple protocol where aromatic acids can undergo C−H exchange with deuterium, using only D_2O as a solvent as well as a source of deuterium. Compared with other methods, this is operationally simple without the need for D_2 gas, or a preinstalled functional group other than hydrogen to replace with deuterium,[28] while utilizing in most cases attractively low loadings of a readily commercially available catalyst. Notably, the reaction can be easily scaled up while maintaining comparable levels of deuteration, making it useful for affordable scale up. Future work in this area may focus on developing catalysts capable of more efficient HDE using fewer equivalents of D_2O, HDO, or even HTO.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02618.

Experimental details and procedures as well as ^1H, ^{13}C NMR, mass spectrometry, and selected ^2H NMR data (PDF)

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Notes

The authors declare no competing financial interest.

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