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Regioselective α-Deuteration of Michael Acceptors Mediated by Isopropylamine in D_2O/AcOD

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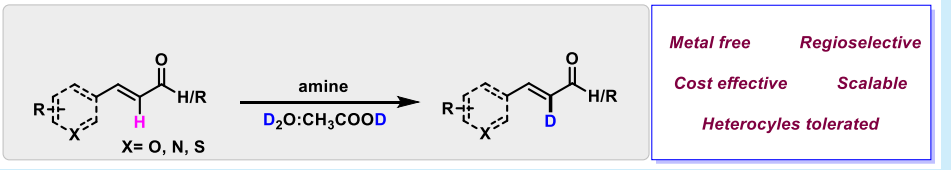

ABSTRACT: Site-specific hydrogen/deuterium exchange is an important method to access deuterated compounds for chemical and biological studies. Herein is reported the first method for the regioselective α-deuteration of enals and enones. The transformation features D_2O and AcOD as deuterium sources and amines as organocatalysts. The deuteration strategy is scalable and works on enals with a variety of substituted arene or heterocycle motifs as well as enones. The method has been applied to the synthesis of deuterated drug precursors.

The sustainable synthesis of deuterated pharmaceutical compounds is gaining momentum in chemical synthesis because replacing hydrogen with deuterium can alter the absorption, distribution, metabolism, and excretion properties of drug candidates while retaining their biological potencies.[1] Deuterium-labeled compounds have found many applications: they serve as useful probes for identifying drug metabolites in vivo[2] and are important for mechanistic studies in organic and metal-catalyzed reactions.[3] Notably, the US Food and Drug Administration has recently cleared deutetrabenzine for use, making it the first drug approved specifically as its deuterated analogue.[4] The synthesis of organic compounds that are selectively labeled with deuterium at nonacidic positions, however, remains a challenging synthetic problem.[5] Recently, nonregioselective synthesis of deuterated molecules has been achieved by using transition-metal catalysts for the deuteration of unactivated aromatic[6] or aliphatic[7] C−H bonds, while the use of directing groups has allowed H/D exchange to occur site-selectively at C−H bonds proximal to the directing group.[8]

Michael acceptors, such as enones and enals, are important building blocks in the synthesis of drugs and natural products. As a result, many methods have been studied for the regioselective deuteration of these species. For example, ruthenium catalysts have been used for the β-deuteration of vinyl carboxylic acids and esters using D_2O and CD_3OD. respectively.[9] Subsequently, our group reported the β-H/D exchange on cinnamic acid derivatives, using low catalyst loadings of rhodium and D_2O as a deuterium source.[10] However, cheap and metal-free approaches toward deuterium incorporation are still sought to reduce the cost of deuterated drugs.[11] Styrenes and cinnamate esters, which are not very electrophilic, can undergo selective α-H/D exchange using organocatalytic systems.[12]

Selective deuteration of enals and enones proves to be more challenging than other Michael acceptors—the presence of multiple sites of reactivity can lead to poor selectivity, while the electrophilicity of the carbonyl can lead to side reactions. In a recent example, NHCs were shown to promote *ipso*-deuteration of aldehydes (Scheme 1a),[13] though yields were improved when the α-position was blocked.

This is because these substrates are known to undergo organocatalyzed reactions such as benzoin condensation and γ-butyrolactone formation unless the α-position is blocked.[14] Notably, this limits the ability of organocatalytic protocols to access H/D exchange at the α-position of these substrates.

More recently, a carbene-catalyzed C−H deuteration reaction of enals was reported that gave high α,γ-selectivity on allylic C(sp^3) and C(sp^2) centers (Scheme 1b).[15] The method, however, was not demonstrated to give the deuterated aldehyde product but rather the carboxylic acid derivatives, and did not work for heterocyclic compounds. As part of our continuing interest in the synthesis of deuterated compounds, we wondered if replacing the NHC catalyst with a weaker nucleophile could facilitate selective α-deuteration while preventing cyclizations that require blocking of the β-position. Instead of reacting at the *ipso* position, a weaker nucleophile would favor conjugate addition, which would allow H/D exchange at the α-position. Herein, we report the first example

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Scheme 1. Organocatalytic Approaches for H/D Exchange of α,β-Unsaturated Aldehydes

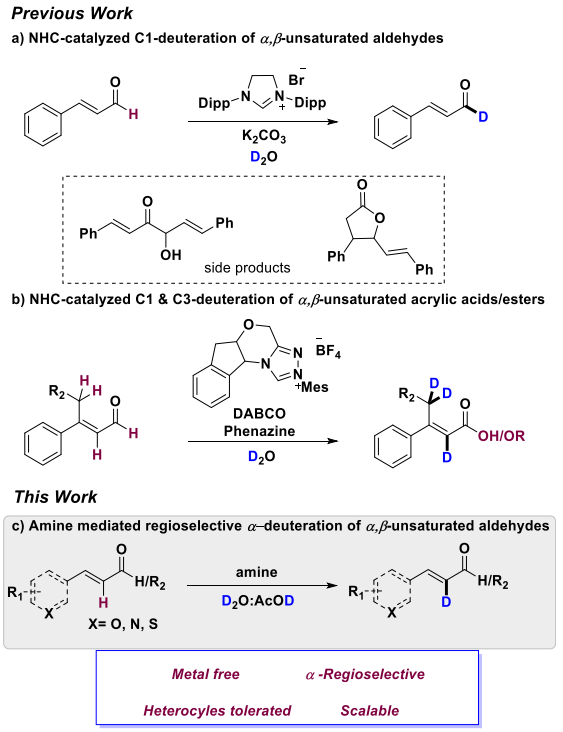
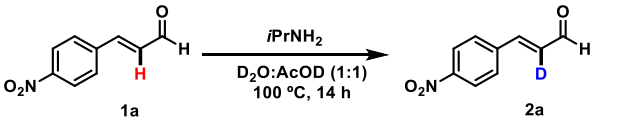


Table 1. Optimization of Reaction Conditions[a]



entry	reaction conditions[a]	D (%)	yield (%)
1	standard conditions	96	97
2	absence of AcOD	0	97
3	no amine	0	98
4	AcOH instead of AcOD	80	96
5	triethylamine used as amine	62	93
6	piperidine used as amine	93	82
7	pyrrolidine used as amine	85	65
8	iPrNH$_2$ (0.5 equiv) used as amine	77	96
9	iPrNH$_2$ (1 equiv) used as amine	90	96
10	iPrNH$_2$ (2 equiv) used as amine	95	97
11	iPrNH$_2$ (3 equiv) used as amine	96	97
12	at 60 °C	0	95
13	at 80 °C	90	93
14	reaction time was 8 h	90	97
15	reaction time was 4 h	70	93
16	THF instead of AcOD	10	35

[a]Reaction conditions: cinnamaldehyde (0.3 mmol), amine (0.9 mmol), and mixture of D$_2$O/AcOD (1:1) 1 mL, heated at 100 °C for 14 h.

of a metal-free regioselective α-deuteration of enals and enones mediated by isopropyl amine using D$_2$O and AcOD as deuterium sources. The deuteration strategy is scalable and works on enals with a variety of substituted arene or heterocycle motifs, as well as acyclic enones (Scheme 1d).

We began our study on the regioselective α-deuteration of enals and other Michael acceptors using 4-nitrocinnamaldehyde (**1a**) as a model substrate and D$_2$O and AcOD as the deuterium sources. AcOD was expected to serve multiple roles, including as a deuterium source, as an acid catalyst, and finally as an organic cosolvent to facilitate dissolution of the substrate in the reaction medium. Initially, **1a** and isopropylamine were combined in a mixture of deuterium oxide and AcOD in a ratio of 1:1, and the reaction mixture was heated at 100 °C (bath temperature) for 14 h to yield the expected product **2a** with 96% deuterium incorporation at the α position in 97% isolated yield (Table 1, entry 1). Gratifyingly, in the present reaction conditions no Baylis−Hillman, lactone dimerization, or aromatic cyclization[16] products were observed.

Notably, deuterium incorporation was not observed in the absence of both acid and amine (entries 2 and 3). Performing the reaction with AcOH instead of AcOD led to a predictable decrease in the levels of deuteration (entry 4). Tertiary and secondary amines were also effective for promoting this deuteration reaction and gave **2a** in moderate yields, albeit with lower deuterium incorporation under the optimized conditions (entries 5−7). The optimal stoichiometry of isopropylamine was also investigated (entries 8−11), although the use of 3 equiv of amine gave the highest level of deuteration and best reproducibility. When the reaction was carried out at 60 °C, we did not observe the expected product because of the low solubility of the substrate (entry 12). The reaction could occur at 80 °C but resulted in lower deuterium incorporation (entry 13). Shortening the time also led to lower levels of H/D exchange (entries 14 and 15). When AcOD was replaced by THF, the reaction was significantly inhibited, demonstrating the need for both an organic solvent as well as an acidic additive (entry 16).

With the optimized conditions in hand (Scheme 2), we set out to probe the versatility of our method in the deuteration of various substituted cinnamaldehydes. Various electron-poor and electron-rich *para*-substituted cinnamaldehydes underwent deuteration at the α-position in good yield (**2a**−**2g**). In the case of **2h**, deuterium incorporation was observed at both the α position and the positions *ortho* to the aniline group, likely caused by acid-mediated S$_E$Ar with D$^+$.[17]

Notably, the reaction could tolerate a S^{VI}-containing substrate and afforded the product **2i** in good yield with nearly full H/D exchange. The reaction scope was further explored for other substituted and unsubstituted cinnamaldehydes, which were all tolerated (**2j**−**2o**). Less soluble π-conjugated substrates were also effectively deuterated (**2p** and **2q**) under the reaction conditions. It is noteworthy that heterocyclic enals such as furfuryl (**2r**), pyrrolyl (**2s**), thiophenyl (**2t**), benzothiophenyl (**2u**), and indolyl (**2v**) also proceeded efficiently and yielded the corresponding deuterated products in good yields. Notably, the lower rate of deuteration (80%) for substrate **2r** could be improved to 90% by allowing the reaction to proceed for an additional 10 h. Perhaps unsurprisingly, in addition to α-deuteration, the electron-rich pyrrolyl group underwent deuteration at every position of the heteroarene (**2s**). Even a ferrocenyl enal could participate in the reaction with good deuterium incorporation, albeit with relatively low recovery due to decomposition. Interestingly, in the cases of **2i** and **2v**, we observed minor deuteration at the *ipso* position, which was confirmed by ^{2}H NMR and high-resolution mass spectrometry. Despite the utility to deuterate aromatic enal substrates, aliphatic enals gave only decomposition products during the reaction.

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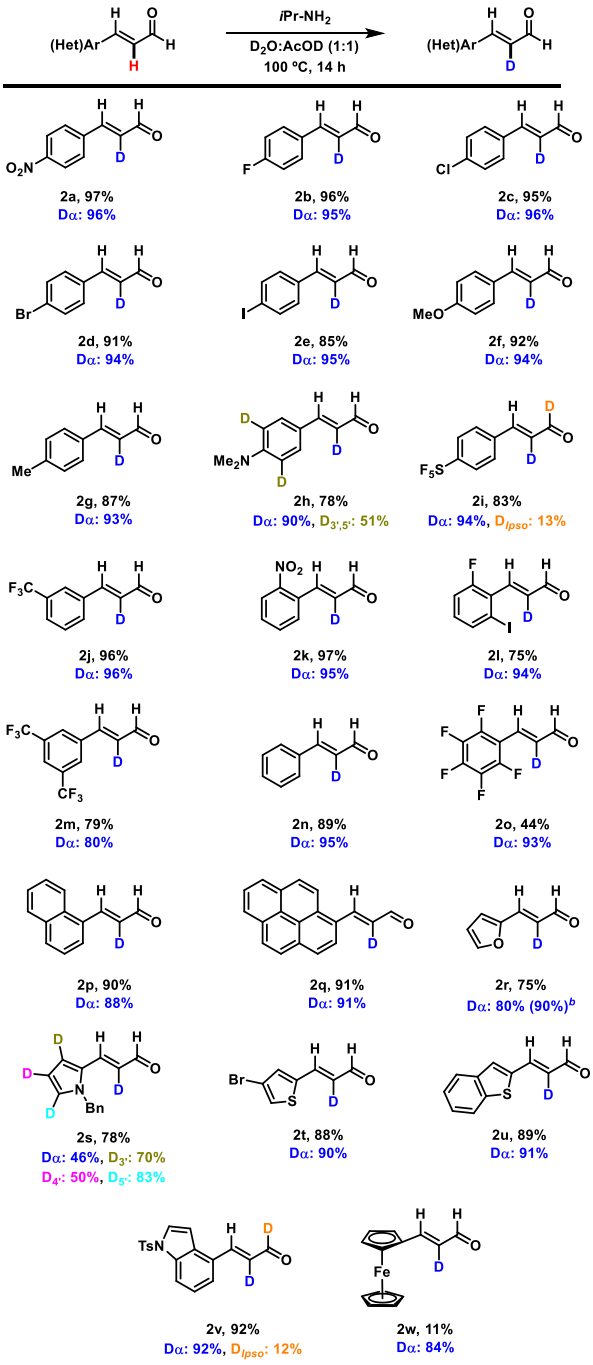
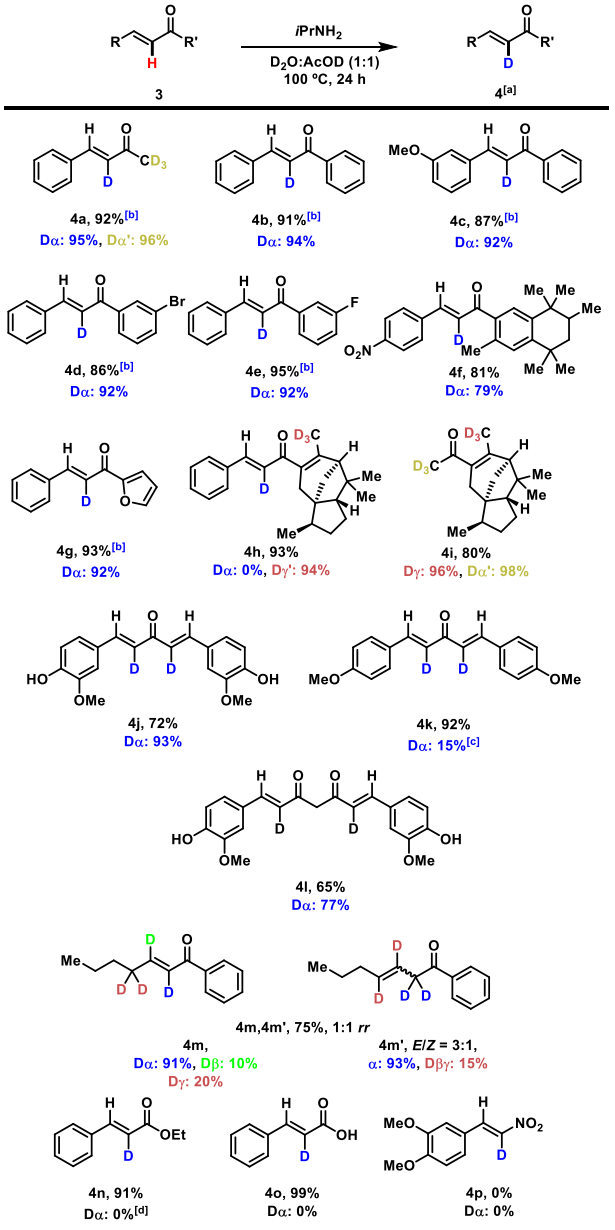
Scheme 2. Substrate Scope for the Deuteration of Enals[a]



[a]Reaction conditions: enal (0.3 mmol), amine (0.9 mmol), and mixture of D_2O/AcOD (1:1) 1 mL, heated at 100 °C for 14 h. Reactions performed in triplicate, and the average yield/deuteration is reported. [b]For 24 h.

Scheme 3. Substrate Scope for the Deuteration of Other Michael Acceptors[a]



[a]Reaction conditions: enal (0.3 mmol), amine (0.9 mmol), and mixture of D_2O/CH_3COOD (1:1) 1 mL, heated at 100 °C for 24 h. Reactions performed in triplicate and the average yield/deuteration reported. [b]Pyridine instead of $iPrNH_2$. [c]Solvent ratio adjusted to D_2O/CH_3COOD/THF (1:1:1) 1.5 mL. [d]D_2O replaced with EtOD.

We next set our sights on other α,β-unsaturated carbonyls (Scheme 3). Commercially available 4-phenylbut-3-en-2-one was deuterated at the α and α'-positions in 49% and 88% conversion, respectively (**4a**), under the standard reaction conditions. For some substrates, including **4a**, we found through reoptimization that addition of pyridine instead of the isopropylamine gave increaseds deuteration at α- and α'-positions in 95% and 96% conversion, respectively (for details, see the SI). The deuteration at α' is due to simple enolization using AcOD. Furthermore, electron-rich and electron-poor substituted chalcones underwent deuteration at the α-position in good yield (**4b**–**4f**). A furfuryl-containing chalcone gave product in good yield with a good amount of deuteration. Surprisingly, in the case of a methyl cedryl ketone derivative, deuteration was observed at the γ'-position, without any observed deuteration at the α-position (**4h**). The same was observed on methyl cedryl ketone, with deuteration at the γ- and α'-positions (**4i**). Notably, our protocol was compatible with a vanillin-based dibenzylidene acetone (**4j**). A less soluble dieneone showed only 6% deuteration and only a slightly improved 15% when an additional 500 μL of tetrahydrofuran was added to aid solubilization (**4k**).

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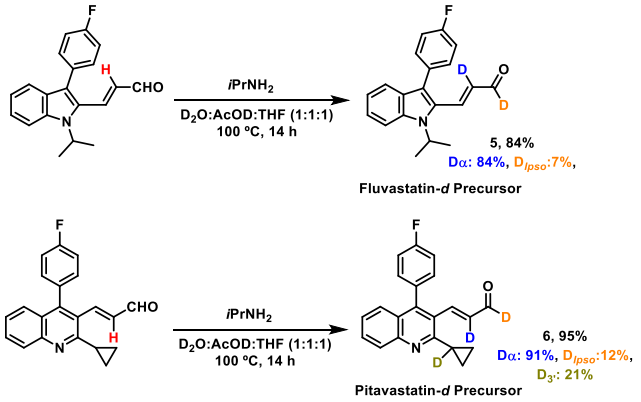
The natural product curcumin could also be subjected to the reaction conditions to give deuteration of the enones (**4l**). In the case of an alkylated aromatic enone, we observed deuteration at the α-position, but also significant isomerization to the β,γ-unsaturated ketone (**4m**). Other α,β-unsaturated Michael acceptors were also used in the reaction. Ethyl cinnamate gave decomposition under the standard conditions, but was returned in good yield with negligible deuteration when D_2O was replaced with EtOD (**4n**). Similarly, cinnamic acid did not undergo deuteration under the reaction conditions (**4o**). Unsurprisingly, a vinyl nitro compound fully decomposed to the aldehyde via a reverse Henry reaction (**4p**).

With a reasonable understanding of the reaction scope, we hoped to demonstrate the applicability toward the synthesis of selectively deuterated drug precursors. A number of statin drugs can be synthesized from enals, including fluvastatin[18] and pitavastatin.[19] As such, we took the commercially available precursor for each and subjected it to our modified conditions with additional tetrahydrofuran added to aid solubility (Scheme 4). The fluvastatin precursor **5** was achieved with

Scheme 4. Approaches for Synthesis of Deuterated α,β-Unsaturated Carbonyl Compounds

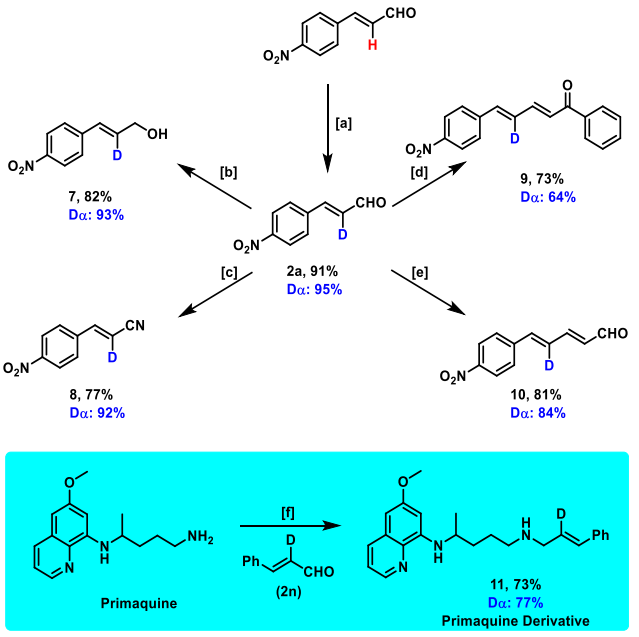


84% deuterium incorporation at the α-position but also with 7% incorporation at the *ipso*-position. The pitavastatin precursor **6** was isolated with 91% deuteration at the α-position, but also a small amount of deuteration at both the *ipso*-position and on the cyclopropyl side chain.

We also wanted to demonstrate that many traditional reactions of enals could occur with retention of the deuterium labeling. First, we attempted to scale up the reaction of the model substrate **1a** (Scheme 5). We were delighted to find that even at 6 mmol scale (20 times the initial scale), the reaction still worked well, despite reducing the ratio of substrate to solvent, giving **2a** in 91% yield with 95% incorporation of deuterium. The reduction of **2a** was achieved in good yield to give **7**, with only minor loss in deuterium labeling. The aldehyde was converted to the nitrile via oxidative amination using iodine and ammonium hydroxide to afford product **8** in 77% yield with 92% deuterium incorporation after the reaction. Furthermore, **2a** was used for condensation reactions to prepare a dieneone (**9**) and dieneal (**10**), though notably with some loss in deuterium labeling. Deuterated primaquine derivative **11** can be easily prepared via the reductive amination of primaquine and **2n**.

In conclusion, we have disclosed a versatile and efficient amine-mediated method for the α-deuteration of α,β-unsaturated aldehydes and ketones using a mixture of

Scheme 5. Scale-Up and Synthetic Applications



[a]Enal (6 mmol), amine (18 mmol), and mixture of D_2O/AcOD (1:1) 10 mL, heated at 100 °C for 24 h. [b]**2a** (1 equiv), $NaBH_4$ (1.5 equiv), MeOH, rt. [c]**2a** (1 equiv), I_2 (1 equiv), aq NH_4OH, rt. [d]**2a** (1 equiv), ketone (1 equiv) NaOH (1.3 equiv) EtOH:H_2O (1:1), rt. [e](i) **2a** (1 equiv), (1,3-dioxolan-2-ylmethyl)triphenylphosphonium bromide (1.5 equiv), 18-crown-6 (2 mol %), K_2CO_3 (1.5 equiv), toluene, 100 °C. (ii) 85% H_3PO_4, THF, 80 °C. [f](i) **2a** (1 equiv), primaquine (1 equiv), $CHCl_3$, 70 °C. (ii) $NaBH_4$ (1.5 equiv), MeOH, RT.

deuterium oxide and acetic acid as a deuterium source. The present methodology has a broad substrate scope and can easily be scaled up for synthetic applications. Significantly, heterocyclic α,β-unsaturated aldehydes were well tolerated. Remarkably, our approach was successfully used for selective α-deuteration of medicinally relevant precursors. A proposed mechanism and supporting experiments can be found in the Supporting Information.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03839.

General information, detailed experimental procedures, and ^1H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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