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Organocatalytic Deuteration Induced by the Dynamic Covalent Interaction of Imidazolium Cations with Ketones

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Abstract: In this article, we suggest a new organocatalytic approach based on the dynamic covalent interaction of imidazolium cations with ketones. A reaction of N-alkyl imidazolium salts with acetone-d_6 in the presence of oxygenated bases generates a dynamic organocatalytic system with a mixture of protonated carbene/ketone adducts acting as H/D exchange catalysts. The developed methodology of the pH-dependent deuteration showed high selectivity of labeling and good chiral functional group tolerance. Here we report a unique methodology for efficient metal-free deuteration, which enables labeling of various types of α-acidic compounds without trace metal contamination.

Keywords: organocatalysis; dynamic covalent chemistry; N-heterocyclic carbenes; pharmaceuticals; deuteration

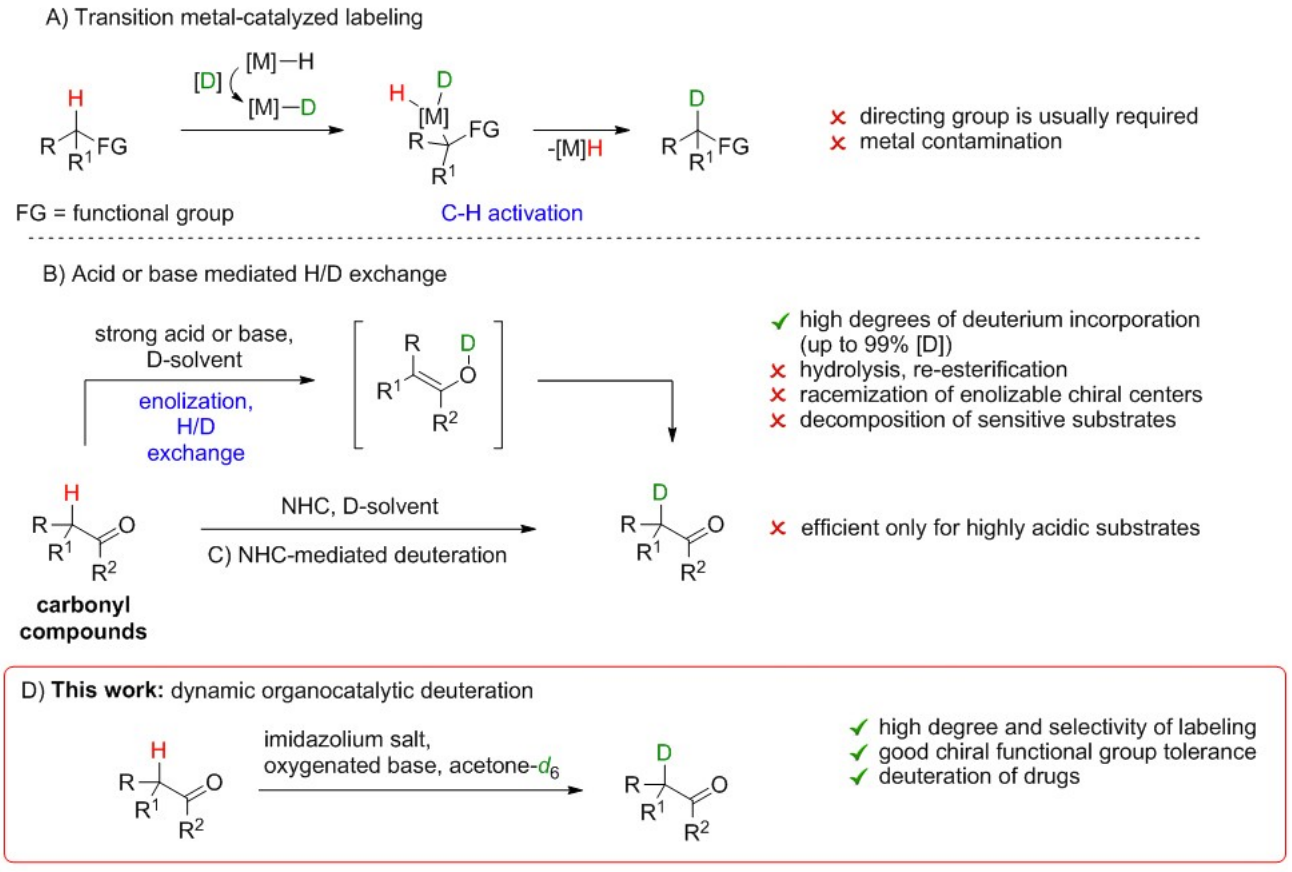
Introduction

Deuterium labeling is a promising synthetic approach that affords new pharmaceuticals with enhanced pharmacokinetic properties and reduced toxicity, whereas the pharmacodynamic properties of deuterated drugs and their non-labeled analogs are generally identical.[1] This is possible because deuterated compounds are metabolized more slowly owing to the increased strength of C–D bonds as compared with C–H bonds.[2] Moreover, deuteration at specific positions in a drug molecule may provide metabolic stabilization of the drug (by causing a reduction in the rate of its degradation) or its safe disposal (by switching its degradation pathways away from toxic metabolites).[3] In 2016, the first deuterated pharmaceutical deutetrabenazine (a derivative of tetrabenazine, deuterated at six hydrogen positions in the two methoxy groups) was approved by FDA.[4] Increasing the half-life of active metabolites allowed to significantly reduce the dose and concomitantly the adverse effects of the drug in Huntington's chorea patients.[5] Leading pharmaceutical companies are now keen on developing deuterated analogs for other drugs, and several clinical trials for deuterated drug candidates are currently underway.[4b,6] Extremely important is to develop metal-free catalytic systems, which would allow deuteration of pharmaceutical substances without metal contamination. Several metal-based catalytic systems suffer from trace metal contamination of the products, where purification to required level (typically <1 ppm of trace metal contamination) is costly and rather difficult to achieve.

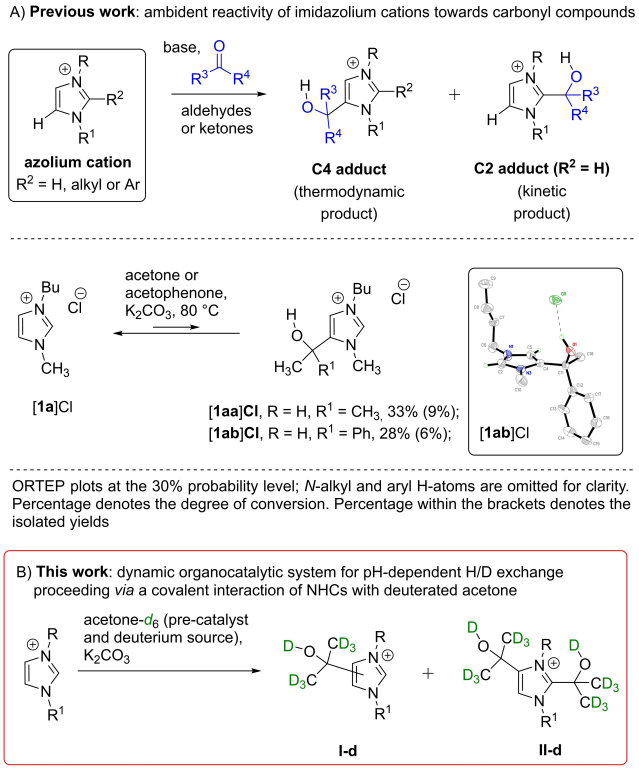
Deuteration of functional groups that are directly involved in drug metabolism is required to achieve desired metabolic effects, and selective post-modification is one of the most efficient approach. In this regard, deuteration at the α-position to pharmacophoric functional groups in drugs and other bioactive compounds without side processes such as racemization or decomposition is an important and challenging task. In some cases, deuteration methods suitable for labeling of drugs should not produce significant effects on sensitive asymmetric centers, since such effects are usually difficult to control. The general approaches to the α-deuteration include transition metal-catalyzed labeling or pH-dependent H/D exchange.[7] The disadvantages of the first approach are the risks of metal contamination and that the introduction of the directing group to the starting substrate is usually required to

achieve the high selectivity of labeling (Scheme 1A). The classical methods of pH-dependent deuteration involve acid- or base-catalyzed H/D exchange between a deuterated solvent and a substrate through the formation of an enolate intermediate in the case of carbonyl compounds (Scheme 1B).[7b,8] For α-deuteration of compounds with low-acidic protons, the presence of strong bases or protic deuterated solvents is generally required,[9] which may be undesirable for the labeling of drugs and other complex substrates due to the side processes such as hydrolysis, racemization, or re-esterification. *N*-heterocyclic carbenes (NHCs) have received significant attention as efficient organocatalysts for medicinal chemistry.[10] Several recent publications demonstrate the successful application of NHCs for the catalysis of H/D exchange, including the labeling of some complex bioactive compounds.[1f,11] However, the organocatalytic pH-dependent deuteration of carbonyl compounds with NHC as a proton shuttle showed high efficiency of labeling only for highly acidic substrates (Scheme 1C).[11c]

In our previous work, we described the ambident reactivity of imidazolium cations towards aldehydes and ketones leading to the formation of a mixture of the C2 and C4 adducts as kinetic and thermodynamic products, respectively (Scheme 2A).[12] This phenomenon, explained by *in situ* generation of the H-bonded abnormal NHCs (*a*NHCs) and the ditopic carbanionic NHCs (*dc*NHCs) along with the classical C2 carbenes from the cationic imidazolium precursors, reflects the dynamic nature of organocatalysis mediated by a covalent interaction of NHCs with carbonyl substrates. In the case of ketones, the formation of the C4 adducts by *a*NHC- and *dc*NHC-based mechanisms was found possible, and the preference for the *dc*NHC pathway was theoretically explained. In particular, we studied the addition of imidazolium cations to acetone and some other ketones in the presence of various bases by high-resolution electrospray ionization mass spectrometry (HRMS-ESI, see Table S1 for details). The strong influence of steric properties of imidazolium salts on their reactivity with ketones was evident: the highest relative intensities of the peaks with (*m/z*) corresponding to the imidazolium cation/ketone adducts were detected for the salts containing α-unbranched *N*-alkyl substituents with chloride or acetate as a counterion.



Scheme 1. General approaches to deuteration of α-acidic compounds: transition metal-catalyzed deuteration (A) or pH-dependent H/D exchange (B–D).



Scheme 2. The dynamic covalent bonding of imidazolium carbenes to carbonyl compounds (possible substituents in the structure **I-d** include deuterated normal (C2) and abnormal (C4 or C5) monoadducts of imidazolium cations with acetone-d_6; in the structure **II-d** include deuterated diadducts of imidazolium cations with acetone-d_6).

For the reaction of some sterically unhindered imidazolium salts with acetone in the presence of potassium carbonate as a base, the peak with (*m/z*) corresponding to diadduct was also detected. "Abnormal" adducts [**1 aa**]Cl and [**1 ab**]Cl formed by the reaction of the ionic liquid 1-butyl-3-methyl-imidazolium chloride ([BMIm]Cl, [**1 a**]Cl) with acetone or acetophenone, respectively, were isolated in pure form and characterized.

In this work, we used these findings for the development of a new organocatalytic approach to the pH-dependent deuteration based on the dynamic covalent interaction of imidazolium carbenes with deuterated acetone (Scheme 1D, Scheme 2B). The catalytic system containing sterically unhindered *N*-alkyl imidazolium salts (as NHC, *dc*NHC or *a*NHC precursors) and acetone-d_6 in the presence of oxygenated bases was efficiently utilized for α-deuteration of model compounds and pharmaceuticals including low acidic substrates (esters, lactones and acetonitrile). The tertiary imidazolium alcohols formed by nucleophilic addition of imidazolium cations to acetone-d_6 at the C2 and C4 carbene centers were identified as H/D transfer mediators in the deuteration process. Steric control of deuterium incorporation by the proposed method was found for the low acidic substrates: efficient labeling of acetate esters, lactones and acetonitrile is opposed to retarded reactivity towards secondary linear and tertiary esters.

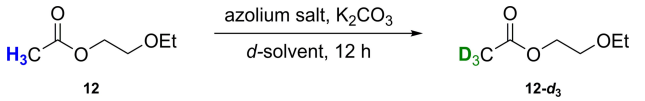
Results and Discussion

We have explored the principal possibility for the development of pH-dependent α-deuteration using a dynamic organocatalytic system based on imidazolium cation/ketone adducts (which are tertiary imidazolium alcohols with labile hydroxyl group) as H/D transfer mediators. Firstly, we applied a catalytic system based on the commercially available imidazolium salts **1 a** [Cl]–**1 c**[Cl] and acetone-d_6 (and, for comparison, some other protic and aprotic deuterated solvents), which served as both an aprotic deuterated solvent and a source for formation of imidazolium alcohols, in the presence of moderately basic oxygenates or amines. Cyclohexanone **7** and 2-ethoxyethyl acetate **12** were chosen as the model substrates (Table 1, Table S3, and Table S4). Most combinations of imidazolium salts, bases and deuterated solvents showed low efficiency of deuteration (Table 1, entries 1–4). As was expected, a combination of [**1 a**]Cl with acetone-d_6 in the presence of oxygenated bases showed the highest catalytic activity for deuteration (entries 6–9).

After optimization of the reaction conditions, products **7**–d_4 and **12**–d_3 were obtained with 97% and 91% degree of substitution in the presence of sodium acetate and potassium carbonate, respectively. For comparison, when deuteration of **12** was performed in the protic deuterated solvents (D_2O or methanol-d_4, entries 4, 5), high efficiency of labeling was achieved in the case of deuterated methanol, but re-esterification was also considerable.

The influence of the nature of imidazolium salt on the efficiency of the H/D exchange was also studied. No deuteration was observed in the presence of salts [**1 b**]Cl and [**1 c**]Cl, which are poorly soluble in acetone (Table 1, entries 2 and 3). Strong influence of steric properties of the catalysts on the degree of deuteration was noted: only the *N*-methyl substituted imidazolium cations $[\mathbf{1\,a}]^+$, $[\mathbf{1\,c}]^+$, and $[\mathbf{1\,d}]^+$, containing α-unbranched substituents at the second nitrogen atom, showed high catalytic activity (entries 8–12). The *N*-ethyl substituted salts [**1 e**]Cl and [**1 f**]Cl showed lower catalytic activity, and no deuteration was observed with the *N*-isopropyl substituted salts [**1 g**]Cl and [**1 h**]Cl (entries 13–15). Similarly, no deuteration occurred in the presence of benzimidazolium salt [**1 i**]Cl and C(4,5)-substituted imidazolium salt [**1 j**]Cl. In contrast, the C2-substituted imidazolium salt [**1 k**]Cl, capable of forming C4 adducts with ketones, showed moderate catalytic activity (entries 16–18). The importance of the nature of counterion was also significant: the

Table 1. Optimization of reaction conditions for the deuteration of esters.



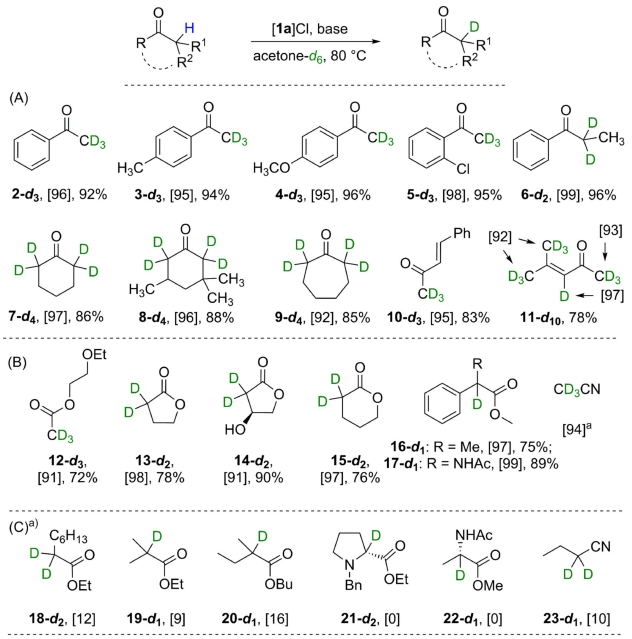
12 **12-d_3**

No	Imidazolium salt	T, °C	Solvent	[D], %[a]
1	[BMIm]Cl, [**1 a**]Cl or [IMes•H]Cl, [**1 b**]Cl	80	$CDCl_3$ or CD_3CN	0–3
2	[**1 b**]Cl	80	acetone-d_6	0
3	[EMIm]Cl, [**1 c**]Cl	80	acetone-d_6	4
4	–	80	D_2O	0[b]
5	–	80	CD_3OD	98[c]
6	[**1 a**]Cl	80	acetone-d_6	13[d]
7	[**1 a**]Cl	60	acetone-d_6	75
8	[**1 a**]Cl	80	acetone-d_6	91
9	[**1 a**]Cl	100	acetone-d_6	84
10	[**1 a**][OAc]	80	acetone-d_6	81
11	[**1 c**][OAc]	80	acetone-d_6	90
12	[HMIm]Cl, [**1 d**]Cl	80	acetone-d_6	76
13	[E_2Im]Cl, [**1 e**]	80	acetone-d_6	37
14	[BEIm]Cl, [**1 f**]	80	acetone-d_6	35
15	[IMIm]Cl, [**1 g**]Cl or [I_2Im]Cl, [**1 h**]Cl	80	acetone-d_6	0
16	[**1 i**]Cl[e]	80	acetone-d_6	0
17	[BM(4,5-M_2)Im]Cl, [**1 j**]Cl	80	acetone-d_6	0
18	[BM(2-E)Im]Cl, [**1 k**]Cl	80	acetone-d_6	33
19	[**1 a**]Br (I^- or $[BF_4]^-$)	80	acetone-d_6	0
20	[**1 a**]Cl	80	acetone-d_6	0[f]
21	–	80	acetone-d_6	0

Reaction conditions: **12** (1 mmol), base (0.2 eq.), azolium salt (0.5 eq.), *d*-solvent (1.5 mL).
[a] Degree of deuteration.
[b] Hydrolysis was detected.
[c] Re-esterification was detected.
[d] Sodium acetate as a base.
[e] 1-Butyl-3-methyl-1*H*-benzimidazolium chloride.
[f] Without base. 1-R-3-R_1-imidazolium salts are denoted as [RR_1Im][anion]; C-substituted 1-R-3-R_1-imidazolium salts are denoted as [$RR_1(R_2)$Im][anion]; M, methyl; E, ethyl; I, isopropyl; B, *n*-butyl; H, *n*-hexyl; IMes, 1,3-bis(2,4,6-trimethylphenyl)-imidazol-2-ylidene. See Supporting Information for more details on the optimization of the reaction conditions.

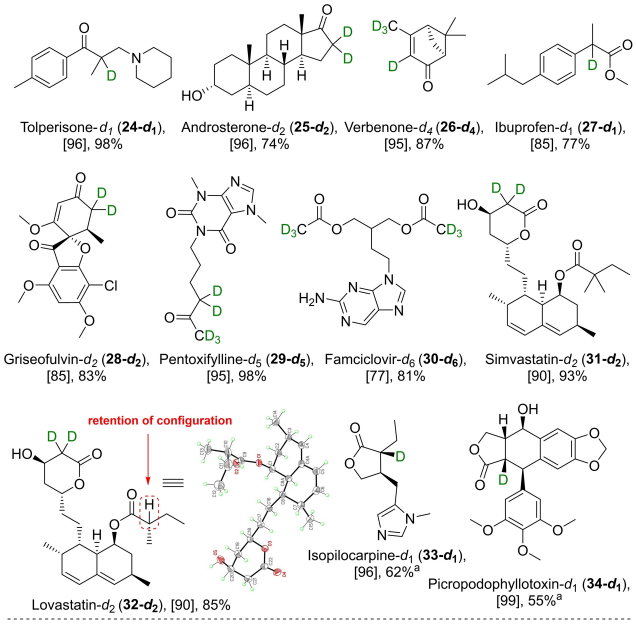
deuteration occurred only with the salts with Cl^- or acetate anion, but not with the salts with Br^-, I^-, or BF_4^- anions (entries 10, 11, and 19). Deuteration of **12** did not proceed without [**1 a**]Cl or in the absence of a base (entries 20, 21).

To study the versatility of the developed catalytic system, we tested a series of model carbonyl compounds and bioactive substances including pharmaceuticals. With slight modifications of the reaction conditions, high degrees of labeling were achieved for the majority of the tested substrates. The desired deuterated products were afforded in moderate to high yields (Scheme 3 and Figure 1). Aryl and alkyl



(A) Scope of ketones. (B) Scope of esters and deuteration of acetonitrile. (C) Compounds deuterated inefficiently. Reaction conditions: substrate (typically, 1 mmol) base (0.2 eq.), [**1a**]Cl (0.5 eq.), acetone-d_6 (typically, 1.5 mL), 80 °C. Potassium carbonate was used as a base for deuteration of compounds **8**, **12-15**, **18-23** and CH_3CN; sodium acetate was used for deuteration of other substrates. Values in square brackets correspond to degrees of deuteration (%). Percent values correspond to isolated yields of the deuterated products. [a] The products were not isolated.

Scheme 3. Deuteration of representative carbonyl-containing compounds and nitriles.



Reaction conditions: substrate (typically, 0.2 mmol), base (0.2 eq.), [**1a**]Cl (0.5 eq.), acetone-d_6 (typically, 0.5-1 mL), 80 °C. Potassium carbonate was used as a base for deuteration of compounds **25**, **28-34**; sodium acetate was used for deuteration of other substrates. Values in square brackets correspond to degrees of deuteration (%). Percent values correspond to isolated yields of the deuterated products. a) Was obtained using 1 eq. of a base.

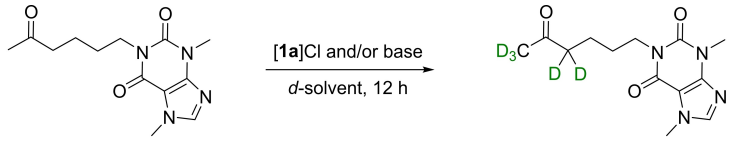
Figure 1. Deuteration of drugs and other bioactive compounds.

ketones, including donor and acceptor acetophenones **2**–**6** and cyclic ketones **7**–**9**, were labeled with > 90% degree of substitution. Similarly, drug molecules containing enolizable keto-groups, including tolperisone **24**, androsterone **25**, were successfully deuterated with > 70% degree of substitution. Enone **10**, verbenone **26** and the fungistatic drug griseofulvin **28** were efficiently and selectively deuterated at the enolizable positions only. Mesityl oxide **11** was fully deuterated with > 90% degree of substitution.

For evaluation of the performance of our organocatalytic approach, we compared labeling of griseofulvin **28** and pentoxyphilline **29** (a precursor for the experimental deuterated phosphodiesterase inhibitor CTP-499) as representative examples by organocatalytic and classical methods based on protic deuterated solvents (Table 2). In the presence of potassium carbonate, all used methods showed more than 90% degree of labeling of pentoxyphilline **29** (entries 11–13). Then sodium acetate was used as a base, compound **29** was deuterated with > 70% efficiency using deuterated methanol or [**1a**][OAc]/acetone-d_6 organocatalytic system (formed *in situ* from [**1a**]Cl and sodium acetate) (entries 8, 9). In the case of deuterated water under the same reaction conditions, the degree of labeling of **29** was significantly lower (13% and 9% of deuterium incorporation in methyl and methylene groups, respectively; entry 10). Such a poor efficiency of the sodium acetate/deuterated water system in the deuteration process in comparison to other used systems may be explained by its lowest basicity (Table S2).

Griseofulvin **28** was unable to undergo deuteration in the presence of sodium acetate or in a deuterated water medium (Table 2, entries 1–3). When potassium carbonate was chosen, an 85% degree of labeling of only enolizable CH_2 group in **28** was achieved using the organocatalytic method (entries 4, 5). In contrast, deuteration of **28** by potassium carbonate in methanol-d_4 at 80 °C result in multiple labeling of both methylene and vinyl protons, re-etherification by deuterated methanol and approximately 32% decomposition (entry 7).

Table 2. Deuteration of pentoxyphilline (**29**) and griseofulvin (**28**) by various methods.



Pentoxyphilline (**29**) Deuterated pentoxyphilline

Griseofulvin (**28**) Deuterated griseofulvin

N°	Substrate	T, °C	Base	Deuteration system	Degree of deuteration [D], %[a]				
					CD_2	CD	CD_3	CD_3'	CD_3''
1	**28**	80	NaOAc	Methanol-d_4 or D_2O	0	0	0	0	0
2	**28**	80	NaOAc	[**1a**]Cl/acetone-d_6	0	0	0	0	0
3	**28**	80	K_2CO_3	D_2O	0	0	0	0	0
4	**28**	60	K_2CO_3	[**1a**]Cl/acetone-d_6	40	0	0	0	0
5	**28**	80	K_2CO_3	[**1a**]Cl/acetone-d_6	85	0	0	0	0
6	**28**	60	K_2CO_3	Methanol-d_4	78	51	21	48	0
7[b]	**28**	80	K_2CO_3	Methanol-d_4	93	94	77	N/A	N/A
8	**29**	80	NaOAc	[**1a**]Cl/acetone-d_6	81	–	73	–	–
9	**29**	80	NaOAc	Methanol-d_4	89	–	88	–	–
10	**29**	80	NaOAc	D_2O	13	–	9	–	–
11	**29**	80	K_2CO_3	[**1a**]Cl/acetone-d_6	95	–	95	–	–
12	**29**	80	K_2CO_3	Methanol-d_4	94	–	92	–	–
13	**29**	80	K_2CO_3	D_2O	98	–	97	–	–

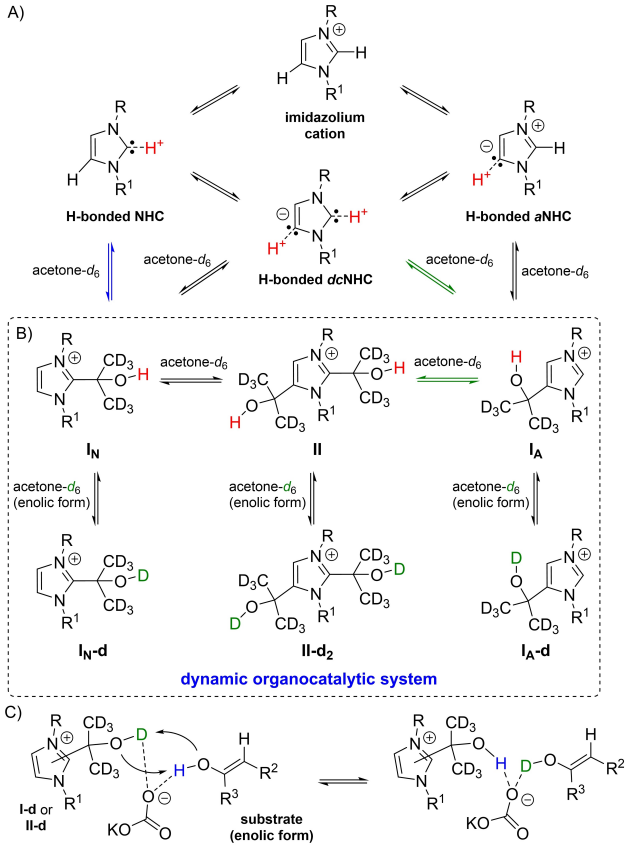
Reaction conditions: substrate (0.2 mmol), base (0.2 eq.), [**1a**]Cl (0.5 eq.), 0.6 mL of solvent.
[a] Was detected by NMR.
[b] Approximately 32% decomposition was observed by NMR.

Decreasing of the reaction temperature to 60 °C led to smaller decomposition of the starting substrate, but the low selectivity of labeling and partial re-etherification were still considerable (entry 6). Thus, the organocatalytic method can show higher efficiency and selectivity of labeling in the case of complex ketonic substrates than the classical approaches based on protic deuterated solvents.

In contrast to reported methods, the deuteration efficiency by our organocatalytic system strongly depended on the acidity and steric properties of the ester substrates. Deuteration of aryl esters **16** and **17** containing a relatively acidic proton at the α-position to the ester group proceeded with a high degree of substitution, accompanied by racemization in the case of optically active substrates. Steric effects were especially pronounced in the deuteration of unactivated esters and nitriles: modifications of acetyl ester **12**, acetonitrile and famciclovir **30** proceeded with 91%, 94% and 77% deuterium incorporation respectively. In contrast to acetyl esters, the more sterically hindered secondary and tertiary esters **18**–**21** and butyronitrile **23** were deuterated with only 9–16% efficiency. Chiral amino acid esters **21** and **22** resisted deuteration (0%). In contrast to the linear secondary and tertiary esters, deuterations of α-unsubstituted lactones **13**–**15** and hypolipidemic drug simvastatin **31** proceeded with high levels of deuterium incorporation. Based on these results, we performed chemoselective deuteration of lovastatin **32** containing both a non-epimerizable lactone and an epimerizable alkyl ester. Labeling of lovastatin at the lactone functional group proceeded with a 90% degree of deuteration. Retention of the configuration and the absence of any modification at α-position in the chiral ester functional group in **32**–d_2 was confirmed by NMR, HPLC and X-ray analysis (see Supporting Information).[13]

The α-substituted diastereomeric lactones pilocarpine and podophyllotoxin were insusceptible to deuteration under the standard conditions but successfully labeled in the presence of 1 eq. of potassium carbonate. The labeling accompanied by stereoinversion at the C3 position[14] yielded the corresponding more thermodynamically stable labeled epimers isopilocarpine **33**–d_1 and picropodophyllotoxin **34**–d_1 with 96% and 99% degrees of deuteration, respectively. Thus, the proposed catalytic system showed high levels of chemoselectivity and chiral functional group tolerance.

According to the mechanistic investigations carried out in the present work and previous study of dynamic reactivity of imidazolium cations towards ketones,[12] a general pathway may be proposed for the deuteration reaction as shown on Scheme 4 (see also Figure S3 for a more details). Relative intensities of the peaks in ESI-MS spectra corresponding to the imidazolium cation/acetone adducts in the reaction mixtures were in accordance with the catalytic activity of corresponding



(A) Generation of the dynamic organocatalytic system and H/D exchange between the imidazolium cation/acetone adducts and the enolic form of deuterated acetone (B). Blue arrows indicate the NHC-based mechanism of the C2 adduct formation (under kinetic reaction conditions). Green arrows indicate the main pathway of the *dc*NHC-based mechanism of formation of the C4 monoadduct and diadduct (under thermodynamic reaction conditions). (C) Concerted mechanism of base-mediated H/D exchange between deuterated adducts **I-d** or **II-d** and enolic form of the ester substrate. All stages are base-mediated. H-bonding with the base is omitted.

Scheme 4. The proposed general mechanism of deuteration.

imidazolium salts in the deuteration process: only imidazolium salts [**1a**]Cl and [**1k**]Cl containing α-unbranched *N*-alkyl substituents (which showed the highest amounts of the imidazolium cation/acetone adducts in the ESI-MS and NMR spectra) has the best catalytic activity in the deuteration process (compare Table 1 and Table S1). Depending on the base used, activation of C2 or C4 positions in the initial imidazolium cation facilitates the formation of H-bonded NHC, *a*NHC or *dc*NHC species. The H-bonded carbene intermediate undergoes nucleophilic addition to deuterated acetone, predominantly by NHC (under kinetic control of the reaction - in the presence of sodium acetate as a base) or *dc*NHC mechanisms (under thermodynamic control of the reaction - in the presence of potassium carbonate as a base and at high temperature) (Scheme 4A). In the second case, this process led to the generation of the dynamic organocatalytic system by reversible formation of the protonated carbene/ketone C4 monoadduct $\mathbf{I_A}$ as the thermodynamic product, as well as few amounts of

diadduct **II** (predominantly *via* the addition of the second molecule of acetone-d_6 to the C4 adduct $\mathbf{I_A}$) and, probably, the C2 monoadduct $\mathbf{I_N}$ (as the kinetic product) (Scheme 4B). According to DFT calculations of pK_a of hydroxyl protons performed for the diadduct **II**, hydroxyl at the "normal" position has 5 orders higher acidity than of the "abnormal" position (see Supporting Information for more details). Thus, despite under the thermodynamic control of the reaction, the adducts containing alcoholic substituents at the C2 position are formed in low amounts, their influence on the efficiency of the deuteration process may be significant.

We suggest that the catalytic activity of imidazolium alcohols in the deuteration process could be related to the acceleration of the deuterium ion transfer from acetone-d_6 to the substrate by fast H/D exchange from the enolic form of deuterated acetone **III** to adducts **I** or **II**, and then from adducts to the substrate **IV**. Low activity of the developed catalytic system towards linear secondary and tertiary esters may be associated with steric factors and explained by the concerted mechanism of H/D exchange between deuterated adducts and the enolic form of ester substrate (Scheme 4C). Difficulties in labeling at the α-CH position in tertiary substituted ketones were recently described for the deuteration with bulky bases.[9b,11b] Chemoselective deuteration at the primary α-CH positions over the secondary and tertiary positions in ester substrates is described for the first time here.

The high catalytic activity of the adducts as H/D exchange mediators and chemoselectivity of the deuteration process are ensured by chemical properties of the adducts, which combine the low nucleophilicity and high mobility of proton of hydroxyl group defined by tertiary structure and the electron-accepting capacity of the cationic imidazolium core. The best efficiency of [**1 a**]Cl as compared to other imidazolium salts for the deuteration process may be explained by the higher reactivity of $[\mathbf{1a}]^+$ towards acetone (see Table S1) and, as a consequence, by the higher concentration of the imidazolium cation/ketone adducts in the reaction mixture.

Conclusion

Ambident reactivity of imidazolium cations represents a previously unexplored type of organocatalysis that proceeds *via* dynamic covalent interaction of imidazolium carbenes with ketones. A new efficient approach to organocatalytic pH-dependent deuteration with the involvement of carbene/acetone-d_6 adducts as H/D exchange mediators is proposed. Applicability of this dynamic organocatalytic system for the deuteration of weakly acidic model compounds and drugs is demonstrated, along with the opportunity to control the selectivity of labeling by modifying the steric properties of the substrates. The first selective deuteration of lovastatin achieved in this study holds promise for the development of deuterated drugs containing base-sensitive chiral centers. Facile access to diverse α-deuterated products enhances the availability of other deuterated drugs and drug candidates.

Experimental Section

General Details. Commercially available starting compounds, reagents, and solvents were of analytical grade upon purchase or purified prior to use by standard methods. Azolium salts were obtained by using published synthetic protocols or purchased commercially. NMR spectra were recorded using a Bruker Fourier 300 HD, Bruker Avance III 400 and Bruker DRX-500 spectrometers at the following frequencies: 300.1/400.1/500.1 MHz (^{1}H), 75.5/100.6/125.8 MHz (^{13}C). ^{13}C{^{2}H} NMR spectrum was recorded using *zgig2h* pulse program. NMR chemical shifts were measured relative to residual solvent peaks. The processing was carried out using the MestReNova software. The following abbreviations were used to describe the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, sept = septet, o = octet, n = nonet, m = multiplet, br = broad. HRMS spectra were recorded on a Bruker maXis instrument equipped with electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI) ion sources. Gas chromatography-mass spectrometry (GC-MS) analysis was performed on an Agilent 5977 A quadrupole instrument using electron ionization (EI) source with sample injection via Agilent 7890 gas chromatograph. HPLC analyses were accomplished using an Agilent 1200 series LC system equipped with a reversed-phase Zorbax SB–C18 Rapid Resolution column (2.1*50 mm, 1.8 μm) thermostated at 25 °C. The mobile phase consisted of 90% MeCN aqueous solution. Merck silica gel plates with a QF-254 indicator were used for analytical TLC. Visualization was accomplished with UV light or by using a solution of $(NH_4)_6Mo_7O_{24}$ and H_2SO_4 in ethanol; the plate was heated until the development of color.

General procedure for deuteration of ketones. Unless indicated otherwise, a mixture of ketone (1 mmol), sodium acetate (16 mg, 0.2 mmol) and [**1 a**]Cl (87 mg, 0.5 mmol) in acetone-d_6 (1.5 mL) was stirred in a sealed tube at 80 °C for 12 h. Then the mixture was filtered through a thin pad of silica gel using $CHCl_3$ as an eluent. The solvents were evaporated at a reduced pressure (300 mbar, bath temperature 50 °C) to give desired deuterated products.

Deuterated acetophenone (2–d_3). The product **2**–d_3 was isolated with a yield of 113 mg (92%) and 96% deuterium incorporation. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98–7.91 (m, 2H), 7.54 (t, J = 7.4 Hz, 1H), 7.44 (t, J = 7.7 Hz, 2H), 2.56 (m, labeled, 0.12H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 198.3, 137.2, 133.2, 128.6, 128.3, 26.0 (labeled). Data in agreement with the literature.[11b]

Deuterated 4-methylacetophenone (3–d_3). The product **3**–d_3 was isolated in a yield of 129 mg (94%) with 95% deuterium incorporation. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, J = 8.1 Hz, 2H), 7.21 (d, J = 8.1 Hz, 2H), 2.50 (m, labeled, 0.14H), 2.36 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 197.9, 143.8,

134.7, 129.2, 128.4, 25.8 (labeled), 21.6. Data in agreement with the literature.[11b]

Deuterated 4-methoxyacetophenone (4–d_3). The product **4**–d_3 was isolated in a yield of 145 mg (96%) with 95% deuterium incorporation. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, J = 8.9 Hz, 2H), 6.88 (d, J = 8.9 Hz, 2H), 3.81 (s, 3H), 2.48 (m, labeled, 0.14H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 196.8, 163.5, 130.6, 130.3, 113.7, 55.4, 25.7 (labeled). Data in agreement with the literature.[11b]

Deuterated 2-chloroacetophenone (5–d_3). The product **5**–d_3 was isolated as a colorless liquid in a yield of 150 mg (95%) with 98% deuterium incorporation. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (dd, J = 7.8, 1.0 Hz, 1H), 7.40–7.32 (m, 2H), 7.29 (td, J = 7.8, 1.6 Hz, 1H), 2.58 (m, labeled, 0.05H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 200.5, 139.1, 132.1, 131.3, 130.7, 129.5, 127.0, 30.0 (labeled).

Deuterated propiophenone (6–d_2). The product **6**–d_2 was isolated in a yield of 130 mg (96%) with 99% deuterium incorporation. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, J = 7.3 Hz, 2H), 7.51 (t, J = 7.3 Hz, 1H), 7.42 (t, J = 7.7 Hz, 2H), 2.94 (m, labeled, 0.01H), 1.18 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 200.9, 136.9, 132.9, 128.6, 128.0, 31.1 (labeled), 8.1. Data in agreement with the literature.[11b]

Deuterated cyclohexanone (7–d_4). A mixture of compound **7** (1.08 mL, 10 mmol), sodium acetate (164 mg, 2 mmol) and [**1a**]Cl (873 mg, 5 mmol) in 15 mL of acetone-d_6 was used. After filtration, product **7**–d_4 was isolated by distillation in vacuo in a yield of 842 mg (86%) with 97% deuterium incorporation. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.24 (m, labeled, 0.10H), 1.79 (m, 4H), 1.66 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 212.5, 41.3 (labeled), 26.9, 24.9. Data in agreement with the literature.[9a]

Deuterated 3,3,5-trimethylcyclohexanone (8–d_4). Potassium carbonate (28 mg, 0.2 mmol) was used as a base. The product **8**–d_4 was obtained as a colorless liquid in a yield of 124 mg (88%) with 96% deuterium incorporation. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.23 (m, labeled, 0.03H), 2.08 (br.s, labeled, 0.05H), 2.00–1.90 (m, 1H + m, labeled, 0.04H, overlapped), 1.82 (m, labeled, 0.04H), 1.53 (dd, J = 13.4, 3.7 Hz, 1H), 1.25 (t, J = 12.9 Hz, 1H), 1.00 (s, 1H), 0.97 (d, J = 6.5 Hz, 3H), 0.83 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 212.2, 53.7 (labeled), 48.6 (labeled), 47.3, 35.3, 32.1, 29.7, 25.8, 22.5.

Deuterated cycloheptanone (9–d_4). The product **9**–d_4 was obtained in a yield of 99 mg (85%) with 92% deuterium incorporation. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.37 (m, labeled, 0.31H), 1.67–1.52 (m, 8H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 215.4, 43.2 (labeled), 30.3, 24.2 (signal corresponds to non-deuterated substrate), 24.1. Data in agreement with the literature.[15]

Deuterated benzylideneacetone (10–d_3). The product **10**–d_3 was isolated as a yellowish oil in a yield of 124 mg (83%) with 95% deuterium incorporation. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58–7.52 (m, 2H), 7.51 (d, J = 16.3 Hz, 1H), 7.42–7.38 (m, 3H), 6.72 (d, J = 16.3 Hz, 1H), 2.36 (m, labeled, 0.15H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 198.6, 143.6, 134.5, 130.6, 129.1, 128.4, 127.3, 27.0 (labeled).

Deuterated mesityl oxide (11–d_{10}). The product **11**–d_{10} was isolated in a yield of 84 mg (78%) with 92%/93%/97% deuterium incorporation. The degree of deuteration was determined by NMR using $PhSiMe_3$ as an internal standard. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.08 (s, labeled, 0.03H), 2.11 (m, labeled, 0.49H), 1.85 (m, labeled, 0.20H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 198.8, 154.9, 124.1 (labeled), 31.0 (labeled), 27.0 (labeled), 21.92–18.20 (labeled).

General procedure for deuteration of esters. Unless indicated otherwise, a mixture of ester (3 mmol), potassium carbonate (84 mg, 0.6 mmol) and [**1a**]Cl (261 mg, 1.5 mmol) in 5 mL of acetone-d_6 was stirred at 80 °C for 12 h. Then the mixture was filtered through a thin pad of silica gel and evaporated at a reduced pressure (300 mbar). The obtained samples of pure products were analyzed by NMR to determine the degree of deuteration.

Deuterated 2-ethoxyethyl acetate (12–d_3). A mixture of compound **12** (1.4 mL, 10 mmol), potassium carbonate (276 mg, 2 mmol) and [**1a**]Cl (873 mg, 5 mmol) in 15 mL of acetone-d_6 was used. After filtration, the product **12**–d_3 was isolated by distillation in vacuo as a colorless liquid in a yield of 0.97 g (72%) with 91% deuterium incorporation. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.15 (t, J = 4.8, 2H), 3.57 (t, J = 4.8 Hz, 2H), 3.47 (q, J = 7.0 Hz, 1H), 2.09–1.98 (m, labeled, 0.28H), 1.15 (t, J = 7.0 Hz, 3H). ^{13}C{H} NMR (101 MHz, $CDCl_3$) δ 171.1, 68.3, 66.6, 63.7, 20.3 (labeled), 15.1.

Deuterated γ-butyrolactone (13–d_2). Product **13**–d_2 was isolated in a yield of 207 mg (78%) with 98% deuterium incorporation. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23 (t, J = 7.1 Hz, 2H), 2.35 (m, labeled, 0.02H), 2.15 (quint, J = 7.1, 2.4, 1.2 Hz, 2H). ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 177.9, 68.6, 27.2 (labeled), 22.0. Data in agreement with the literature.[9e]

Deuterated (*S*)-4-hydroxydihydrofuran-2(3H)-one (14–d_2). The product obtained under standard conditions was treated with water. Compound **14**–d_2 was isolated as a colorless liquid in a yield of 280 mg (90%) with 91% deuterium incorporation. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.63 (br.d, J = 3.8 Hz, 1H), 4.39 (dd, J = 10.3, 4.3 Hz, 1H), 4.27 (dd, J = 10.3, 1.0 Hz, 1H), 3.55 (s, 1H), 2.70 (m, labeled, 0.09H), 2.45 (br.s, labeled, 0.09H). ^{13}C{H} NMR (75 MHz, $CDCl_3$) δ 177.3, 76.5, 67.3, 37.3 (labeled).

Deuterated δ-valerolactone (15–d_2). Product **15**–d_2 was isolated in a yield of 234 mg (76%) with 97% deuterium incorporation. ^{1}H NMR (300 MHz, acetone-d_6) δ 4.28 (m, 2H), 2.45 (m, labeled, 0.05H), 1.82 (m, 4H). ^{13}C{H} NMR (75 MHz, CD_2Cl_2) δ 171.5, 69.8, 29.5 (labeled), 22.7, 19.3. Data in agreement with the literature.[16]

Deuterated racemic methyl 2-phenylpropanoate (16–d_1). (R)-Methyl 2-phenylpropanoate or racemic methyl 2-phenylpropanoate were used. Product **16**–d_1 was isolated in a yield of 371 mg (75%) with **97**% deuterium incorporation. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.18 (m, 5H), 3.73 (q, labeled, 0.03H), 3.66 (s, 3H), 1.50 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 175.1, 140.6, 128.8, 127.6, 127.3, 52.1, 45.2 (labeled), 18.6. Data in agreement with the literature.[17]

Deuterated racemic methyl 2-acetamido-2-phenylacetate (17–d_1). *R*-enantiomer or racemic mixture of compound **17**

were used. The product **17**–d_1 was isolated as a white solid in a yield of 555 mg (89%) with 99% deuterium incorporation. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (m, 5H), 6.71 (br.s, 1H), 5.58 (d, J = 7.3 Hz, labeled, 0.02H), 3.71 (s, 3H), 2.01 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 171.5, 169.8, 136.4, 129.1, 128.7, 127.4, 56.2 (labeled), 52.9, 23.0.

Synthesis of deuterated tolperisone (24–d_1). A mixture of tolperisone **24** (49 mg, 0.2 mmol), sodium acetate (3.3 mg, 0.04 mmol) and [**1 a**]Cl (18 mg, 0.1 mmol) in 0.5 mL of acetone-d_6 was stirred at 80 °C for 12 h. The reaction mixture was then diluted with chloroform and filtered through a short pad of silica gel using $CHCl_3$:MeOH, 10:1 as an eluent. The solvents were evaporated under reduced pressure to give 48 mg of product **24**–d_1 as a colorless oil (98% yield, 96% deuterium incorporation). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, J = 8.2 Hz, 2H), 7.25 (d, J = 8.1 Hz, 2H), 3.74 (m, labeled, 0.04H), 2.84 (d, J = 12.5 Hz, 1H), 2.39 (m, 8H), 1.50 (m, 4H), 1.36 (m, 2H), 1.16 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 203.6, 143.7, 134.4, 129.4, 128.6, 62.2, 55.0, 38.4 (labeled), 25.9, 24.3, 21.7, 16.9.

Synthesis of deuterated androsterone (25–d_2). A mixture of androsterone **25** (106 mg, 0.4 mmol), potassium carbonate (11 mg, 0.08 mmol) and [**1 a**]Cl (36 mg, 0.2 mmol) in 1 mL of acetone-d_6 was stirred at 80 °C for 12 h. The reaction mixture was then diluted with chloroform and filtered through a short pad of silica gel using $CHCl_3$:MeOH, 20:1 as an eluent. The solvents were evaporated under reduced pressure to give 78 mg of product **25**–d_2 as a white powder (74% yield, 96% deuterium incorporation). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.02 (m, 1H), 2.37 (m, labeled, 0.04H), 2.13 (d, J = 12.0 Hz, labelled, 0.04H), 1.90 (m, 2H), 1.76 (m, 2H), 1.67–1.14 (m, 15H), 1.00 (m, 1H), 0.82 (s, 3H), 0.80 (m, 1H), 0.77 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 221.7, 66.4, 54.5, 51.6, 47.9, 39.2, 36.3, 35.9 (labeled) 35.8, 35.1, 32.2, 31.6, 30.9, 29.0, 28.3, 21.6, 20.1, 13.9, 11.3. Data in agreement with the literature.[18]

Synthesis of deuterated verbenone 26–d_4. A mixture of (*S*)-(-)-verbenone **26** (30 mg, 0.2 mmol), sodium acetate (3.3 mg, 0.04 mmol) and [**1 a**]Cl (18 mg, 0.1 mmol) in 0.5 mL of acetone-d_6 was stirred at 80 °C for 12 h. The reaction mixture was then diluted with chloroform and filtered through a short pad of silica gel using $CHCl_3$:MeOH, 20:1 as an eluent. The solvents were evaporated under reduced pressure to give 26 mg of compound **26**–d_4 as a colorless liquid (87% yield, 95% deuterium incorporation). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71 (s, labeled, 0.05H), 2.79 (dt, J = 9.2, 5.5 Hz, 1H), 2.63 (t, J = 5.5 Hz, 1H), 2.40 (t, J = 5.9 Hz, 1H), 2.06 (d, J = 9.2 Hz, 1H), 1.96 (m, labeled, 0.14H), 1.48 (s, 3H), 0.99 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 204.2, 170.2, 121.0 (labeled), 57.7, 54.2, 49.7, 41.0, 26.7, 22.8 (labeled), 22.2.

Synthesis of deuterated ibuprofen (27–d_1). A mixture of ibuprofen **27** (44 mg, 0.2 mmol), sodium acetate (3.3 mg, 0.04 mmol) and [**1 a**]Cl (18 mg, 0.1 mmol) in 0.5 mL of acetone-d_6 was stirred at 80 °C for 12 h. The reaction mixture was then diluted with chloroform and filtered through a short pad of silica gel using $CHCl_3$ as an eluent. The solvents were evaporated under reduced pressure to give 34 mg of compound **27**–d_1 as a colorless oil (77% yield, 85% deuterium incorporation). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (d, J = 8.1 Hz, 2H), 7.10 (d, J = 8.1 Hz, 2H), 3.71 (m, labeled, 0.15H), 3.66 (s, 3H), 2.46 (d, J = 7.2 Hz, 2H), 1.86 (n, J = 6.8 Hz, 1H), 1.49 (s, 3H), 0.91 (d, J = 6.8 Hz, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 175.3, 140.7, 137.8, 129.5, 127.2, 52.1, 45.2, 44.8 (labeled), 30.3, 22.5, 18.6. Data in agreement with the literature.[17]

Synthesis of deuterated grizeofulvin. Method A: a mixture of grizeofulvin **28** (70 mg, 0.2 mmol), potassium carbonate (5.5 mg, 0.04 mmol) and [**1 a**]Cl (18 mg, 0.1 mmol) in 0.5 mL of acetone-d_6 was stirred at 80 °C for 12 h. The reaction mixture was then diluted with chloroform and washed by water. Removal of the solvents afforded 65 mg of compound **28**–d_2 as a yellowish powder (93% yield, 85% deuterium incorporation). **Method B**: a mixture of grizeofulvin **28** (70 mg, 0.2 mmol), potassium carbonate (5.5 mg, 0.04 mmol) in 0.5 mL of methanol-d_4 was stirred at 60 °C or 80 °C for 12 h. The degree of deuteration was determined by NMR. ^{1}H NMR (300 MHz, CD_2Cl_2) δ 5.99 (s, 1H), 5.51 (s, 1H), 4.02 (s, 3H), 3.96 (s, 3H), 3.62 (s, 3H), 2.89 (m, 0.20H, labeled), 2.79 (q, J = 6.2 Hz, 1H), 2.37 (m, labeled, 0.10H), 0.91 (d, J = 6.7 Hz, 3H). ^{13}C{H} NMR (75 MHz, CD_2Cl_2) δ 196.7, 192.3, 171.1, 169.8, 165.0, 158.2, 105.4, 105.1, 97.2, 91.0, 90.1, 57.5, 57.2, 56.8, 40.0 (labeled), 36.77 (signal correspond to non-deuterated substrate), 36.70, 14.3.

Synthesis of deuterated pentoxifylline (29–d_5). Method A: a mixture of pentoxifylline **29** (56 mg, 0.2 mmol), base (0.04 mmol) and [**1 a**]Cl (18 mg, 0.1 mmol) in 0.5 mL of acetone-d_6 was stirred at 80 °C for 12 h. The reaction mixture was then diluted with chloroform and filtered through a short pad of silica gel using $CHCl_3$:MeOH, 20:1 as an eluent. Removal of the solvents followed by washing with Et_2O afforded 55 mg of compound **29**–d_5 as a white powder (98% yield, 73% (CD_3) and 81% (CD_2) deuterium incorporation using sodium acetate as a base; 93% yield, 95% (CD_3) and 95% (CD_2) deuterium incorporation using potassium carbonate as a base). **Method B**: a mixture of pentoxifylline **29** (56 mg, 0.2 mmol) and base (0.04 mmol) in 0.5 mL of deuterated solvent was stirred at 80 °C for 12 h. The degree of deuteration was determined by NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (s, 1H), 3.92 (m, 5H), 3.49 (s, 3H), 2.40 (m, labeled, 0.10H), 2.04 (m, labeled, 0.14H), 1.56 (m, 4H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 209.0, 155.2, 151.4, 148.6, 141.5, 107.6, 42.4 (labeled), 40.8, 33.6, 29.7, 29.2 (labeled), 27.4, 20.8. Data in agreement with the literature.[19]

Synthesis of deuterated famciclovir (30–d_6). A mixture of famciclovir **30** (96 mg, 0.3 mmol), potassium carbonate (16.5 mg, 0.12 mmol) and [**1 a**]Cl (27 mg, 0.15 mmol) in 1 mL of acetone-d_6 was stirred at 60 °C for 12 h. The reaction mixture was then diluted with chloroform and filtered through a short pad of silica gel using $CHCl_3$:MeOH, 20:1 as an eluent. Removal of the solvents followed by washing with Et_2O afforded 78 mg of compound **30**–d_6 as a light-yellow powder (81% yield, 77% deuterium incorporation). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (s, 1H), 7.76 (s, 1H), 5.22 (br.s, 2H), 4.17 (t, J = 7.0 Hz, 2H), 4.10 (d, J = 5.2 Hz, 4H), 1.98 (m, labeled, 1.37H), 2.03–1.85 (m, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 171.0, 159.7, 153.5, 149.3, 142.5, 128.2, 63.7, 40.9, 35.0, 28.9, 20.4 (labeled).

Synthesis of deuterated simvastatin (31–d_2). A mixture of simvastatin **31** (84 mg, 0.2 mmol), potassium carbonate (5.5 mg, 0.04 mmol) and [**1 a**]Cl (18 mg, 0.1 mmol) in 1 mL of

acetone-d_6 was stirred at 80 °C for 12 h. The solvents were evaporated and the reaction mixture was purified by column chromatography on silica gel using $CHCl_3$:MeOH, 30:1. Removal of the solvents followed by washing with Et_2O afforded 78 mg of compound **31–d_2** as a white powder (93% yield, 90% deuterium incorporation). ^{1}H NMR (300 MHz, CD_2Cl_2) δ 5.99 (d, J = 9.7 Hz, 1H), 5.79 (dd, J = 9.5, 6.1 Hz, 1H), 5.51 (m, 1H), 5.34 (q, J = 3.1 Hz, 1H), 4.58 (m, 1H), 4.33 (t, J = 3.5 Hz, 1H), 2.65 (m, labeled, 0.10H), 2.53 (m, labeled, 0.10H), 2.39 (m, 2H), 2.28 (m, 1H), 1.94 (m, 3H), 1.82 (m, 1H), 1.67 (m, 2H), 1.61–1.43 (m, 3H), 1.43–1.22 (m, 3H), 1.112 (s, 3H), 1.107 (s, 3H), 1.08 (d, J = 7.4 Hz, 3H), 0.89 (d, J = 7.0 Hz, 3H), 0.82 (t, J = 7.5 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 178.2, 170.7, 133.0, 131.6, 129.8, 128.5, 76.6, 68.2, 62.6, 43.2, 38.4 (labeled), 37.6, 36.7, 36.2, 33.11, 33.06, 33.0, 30.8, 27.4, 24.9, 24.4, 23.2, 14.0, 9.5.

Synthesis of deuterated lovastatin 32–d_2. A mixture of lovastatin **32** (81 mg, 0.2 mmol), potassium carbonate (11 mg, 0.08 mmol) and [**1a**]Cl (18 mg, 0.1 mmol) in 1 mL of acetone-d_6 was stirred at 80 °C for 12 h. The reaction mixture was then diluted with chloroform and filtered through a short pad of silica gel using $CHCl_3$:acetone, 10:1 as an eluent. Removal of the solvents followed by washing with Et_2O afforded 69 mg of compound **32–d_2** as a white powder (85% yield, 90% deuterium incorporation). ^{1}H NMR (300 MHz, CD_2Cl_2) δ 5.98 (d, J = 9.7 Hz, 1H), 5.79 (dd, J = 9.6, 6.1 Hz, 1H), 5.52 (br.s, 1H), 5.35 (m, 1H), 4.58 (m, 1H), 4.33 (s, 1H), 2.65 (m, labeled, 0.15H), 2.53 (m, labeled, 0.05H), 2.47–2.25 (m, 5H), 2.05–1.76 (m, 4H), 1.75–1.55 (m, 3H, overlapped with residual water), 1.53–1.23 (m, 4H), 1.08 (m, J = 6.7 Hz, 6H), 0.89 (m, 3H), 0.86 (m, 2H). ^{13}C{^{1}H} NMR (75 MHz, CD_2Cl_2) δ 176.9, 170.5, 133.5, 132.1, 130.0, 128.6, 76.6, 68.2, 62.9, 41.9, 38.7 (labeled), 37.6, 37.0, 3.5, 33.3, 33.0, 31.1, 28.0, 27.3, 24.5, 23.0, 16.4, 14.0, 12.0.

Synthesis of deuterated isopilocarpine (33–d_1). A mixture of pilocarpine **33** (42 mg, 0.2 mmol), potassium carbonate (11 mg, 0.08 mmol) and [**1a**]Cl (36 mg, 0.2 mmol) in 0.5 mL of acetone-d_6 was stirred at 80 °C for 12 h. The reaction mixture was then diluted with chloroform and filtered through celite. The solvents were evaporated and the reaction mixture was purified by column chromatography on silica gel using $CHCl_3$:MeOH, 20:1 as an eluent to give 29 mg of compound **33–d_1** containing ~10% of non-reacted pilocarpine (colorless oil, 62% yield, 96% deuterium incorporation). ^{1}H NMR (300 MHz, $CDCl_3$, description of signals of non reacted pilocarpine are omitted) δ 7.58 (s, 1H), 6.83 (s, 1H), 4.39 (dd, J = 9.4, 7.1 Hz, 1H), 3.91 (dd, J = 9.4, 6.6 Hz, 1H), 3.60 (s, 3H), 2.82 (dd, J = 15.1, 5.4 Hz, 1H), 2.72–2.53 (m, 2H), 1.72 dq, J = 7.4, 2.0 Hz, 2H), 1.02 (t, J = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 178.4, 138.2, 128.7, 126.1, 71.1, 46.2 (labeled), 39.0, 31.7, 27.5, 22.4, 11.2. Data in agreement with the literature.[20]

Synthesis of deuterated picropodophyllotoxin 34–d_1. A mixture of podophyllotoxin **34** (41 mg, 0.1 mmol), potassium carbonate (14 mg, 0.1 mmol) and [**1a**]Cl (18 mg, 0.1 mmol) in 0.5 mL of acetone-d_6 was stirred at 80 °C for 12 h. The reaction mixture was then diluted with chloroform and filtered through celite. The solvents were evaporated and the reaction mixture was purified by column chromatography on silica gel using $CHCl_3$:acetone, 3:1 as an eluent. After recrystallization from acetone-Et_2O, the product was treated with H_2O to give 22 mg of compound **34–d_1** as a colorless powder (55% yield and 99% deuterium incorporation). ^{1}H NMR (300 MHz, acetone-d_6) δ 7.15 (s, 1H), 6.65 (s, 2H), 6.18 (s, 1H), 5.93 (s, 1H), 5.91 (s, 1H), 5.07 (d, J = 6.3 Hz, 0.51H, OH), 4.58 (dd, J = 9.3, 1.3 Hz, 1H), 4.51 (dd, J = 9.8, 6.1 Hz, 1H), 4.44 (dd, J = 9.3, 6.1 Hz, 1H), 3.96 (s, 1H), 3.80 (s, 6H), 3.74 (s, 3H), 3.40 (m, 0.01H, labeled, overlapped with Et_2O), 2.67 (dd, J = 9.8, 6.3 Hz, 1H). ^{13}C{^{1}H} NMR (75 MHz, acetone-d_6) δ 178.4, 154.6, 147.4, 147.3, 140.2, 135.4, 132.4, 108.8, 107.5, 105.6, 101.8, 70.1, 68.9, 68.8, 60.5, 56.5, 45.6 (labeled), 44.9, 44.0.

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