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Radical Deuteration

Remote Site-Selective Radical C(sp^3)–H Monodeuteration of Amides using D_2O

*Lin Wang[+], Yong Xia[+], Volker Derdau, and Armido Studer**

Abstract: *Site-selective incorporation of deuterium into biologically active compounds is of high interest in pharmaceutical industry. We present a mild and environmentally benign metal-free method for the remote selective radical C–H monodeuteration of aliphatic C–H bonds in various amides with inexpensive heavy water (D_2O) as the deuterium source. The method uses the easily installed N-allylsulfonyl moiety as an N-radical precursor that generates the remote C-radical via site-selective 1,5- or 1,6-hydrogen atom transfer (HAT). Methyl thioglycolate, that readily exchanges its proton with D_2O, serves as the radical deuteration reagent and as a chain-carrier. The highly site-selective monodeuteration has been applied to different types of unactivated sp^3-C–H bonds and also to the deuteration of C–H bonds next to heteroatoms. The potential utility of this method is further demonstrated by the site-selective incorporation of deuterium into natural product derivatives and drugs.*

Introduction

Deuteration is valuable for organic synthesis,[1] mechanistic investigations[2] and spectrometric/scopic analysis.[3] Considering drug discovery, the biological profile of a given compound can be altered after deuteration, and deuterated analogues of drugs or drug candidates provide a diagnostic tool, addressing the metabolic profile of a drug both in vivo and in vitro.[4] The precise introduction of an isotopic label in a metabolically stable position is essential for the application of deuterium-labelled compounds in vivo, which is of great advantage to anchor the deuterium selectively at a chemically and enzymatically unreactive site to limit degradation during metabolism of the pharmaceutical drug. Because proximal deuterium can be swiftly trimmed by phase I metabolism, for example, oxidation and hydrolysis, a distally labelling position to activate heteroatoms in the molecule is potentially enhancing the metabolic stability of the deuterated compound in vivo.[5] In 2017, the FDA approved the first deuterated drug, deutetrabenazine, a fact that should further motivate organic chemists to develop novel deuteration methods for the efficient synthesis of deuterated drugs and their key building blocks.[6] In these cases, deuteration is preferentially requested at C–H sites that are readily oxidized during metabolism.

In general, selective deuterium-labelling of a pharmaceutical compound requires tedious multistep procedures.[7] Direct hydrogen isotope exchange (HIE) in a given compound at various C–H bonds is challenging but would be highly valuable for late-stage introduction of deuterium.[8] Along these lines, transition metal-catalyzed HIE reactions have been developed for deuteration of aromatic C(sp^2)–H bonds.[9] Although, aliphatic C(sp^3)-H moieties are highly abundant in organic compounds, the direct selective HIE of aliphatic C–H bonds has not been well investigated. Therefore, a general and practical HIE reaction of C(sp^3)–H bonds enabling high D-incorporation ideally site-selectively at activated as well as at unactivated positions is highly desirable for the pharmaceutical industry.[10]

Aliphatic amines and carboxylic acids can be found in many pharmaceutical drugs, in natural products and as bulk chemicals. The selective incorporation of deuterium at a distal unactivated C(sp^3)-H site in a complex amine or acid is very challenging, since such compounds generally contain multiple C–H sites where many of them are more activated than their inert aliphatic C–H positions. Deuterated analogues of these amines and acids could serve as important building blocks to construct value-added deuterium-labelled molecules.[11] Furthermore, mono-deuteration is indeed a rarely applied concept in life sciences and the effect of -CHD- groups on oxidative metabolism enzymes is unknown at present. The development of a site-selective mono-deuteration for aliphatic amines and carboxylic acids would provide a valuable tool, targeting the study of metabolic pathways of endogenous substrates and xenobiotics as well as the optimization of pharmacokinetic and pharmacodynamic parameters of drugs.[12]

Applying a directing group strategy, transition metal catalyzed HIE reaction of aliphatic C–H bonds is a common way to access α- and β-deuterated amines and alcohol derivatives.[10] The MacMillan group recently reported an elegant photoredox-catalyzed deuteration at α-amino C(sp^3)–H bonds.[13a] However, site-selective mono-deuteration at distal unactivated sites remains challenging using existing methodology.[10,13] The Hoffmann-Löffler-Freytag (HLF) re-

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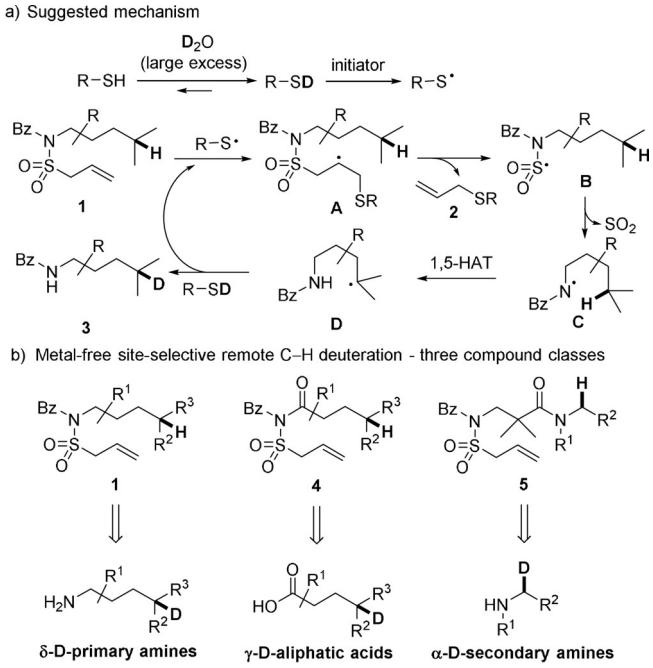
action and variants thereof reliably allow for remote site-selective generation of C-radicals at unactivated sites via 1,5 hydrogen atom transfer (HAT).[14,15] On that basis, our group has recently achieved remote C–H functionalization of unactivated C–H bonds in amides with various sulfones by using the readily installed N-allylsulfonyl moiety as the N-radical precursor.[16,17] Encouraged by these results, we decided to use such N-allylsulfonamides as substrates in combination with a thiol in the presence of D_2O for remote site-selective radical C–H deuteration.[13a,18] Our reaction design with the underlying suggested mechanism for the remote radical C(sp^3)-H deuteration of N-allylsulfonamides **1** is depicted in Scheme 1a.

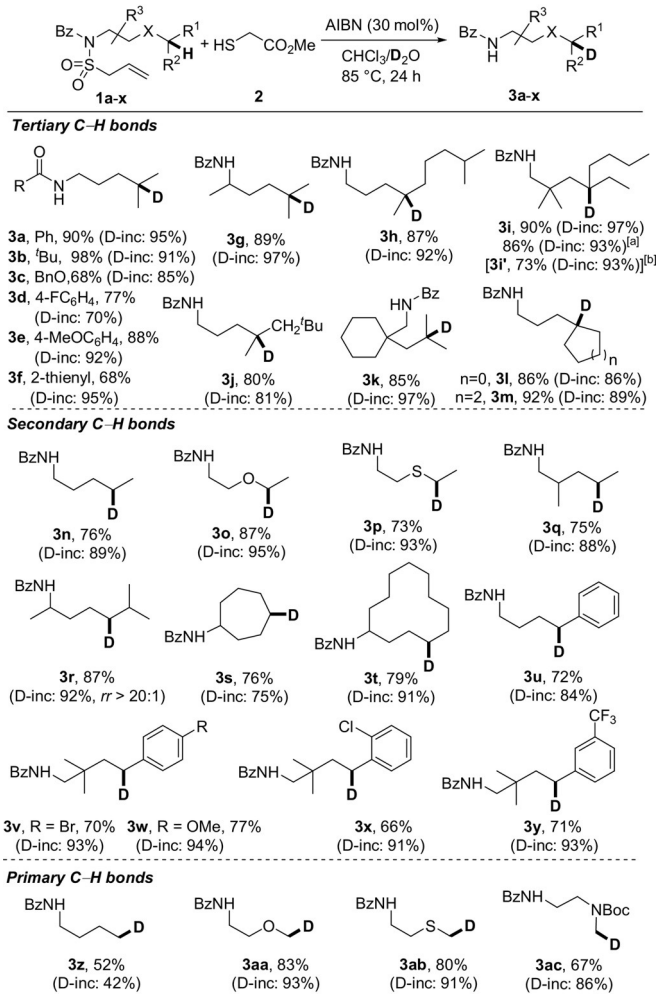


Scheme 1. Remote HIE reaction of C(sp^3)–H bonds.

A thiol R-SH will quickly exchange its proton by D with D_2O (excess) to give the D-labelled thiol R-SD. Initiation of the radical chain leads to a thiyl radical. Such S-centered radicals reversibly add[19] to the terminal double bond of the allylsulfonyl moiety in amide **1** to give the adduct radical **A**. This secondary radical **A** then undergoes β-fragmentation to give the allyl sulfide **2** along with the amidosulfonyl radical **B**. After releasing SO_2, the thus generated N-radical **C** engages in a 1,5-HAT to afford the nucleophilic C-radical **D**, which is readily reduced by R-SD to afford the deuterated amide **3** and the chain carrying thiyl radical. Notably, due to polar effects,[19b] the direct reduction of the electrophilic amidyl radical by the "electrophilic" D-donor R-SD should be slow. Moreover, unwanted addition of the chain carrying thiyl radical to the allylsulfide byproduct **2** is a degenerate process that does not lead to any chain termination.[20] By using this strategy, we expected to access three different types of deuterium-labelled compounds, including δ-D-primary amines, γ-D-aliphatic acids and α-D-secondary amines from the corresponding readily prepared precursors **1**, **4** and **5** (Scheme 1b).

Results and Discussion

We started our investigations by using the sulfonamide **1a** as the model substrate (Scheme 2). Optimization revealed that reaction is best conducted with methyl thioglycolate **2** as the R-SD precursor (1.1 equiv) and α,α′-azobisisobutyronitrile (AIBN) as the radical initiator in $CHCl_3/D_2O$ (v/v 2:1) at elevated temperature to afford the remote deuterated amide **3a** with excellent yield (90%) and high level of D-incorporation (95%, as determined by mass spectrometry analysis). Other thiols, such as thiophenol, 2-propanethiol, 1-decanethiol, thiobenzoic acid and triisopropylsilane thiol led to lower yields and lower D-incorporation under the same



Scheme 2. Remote site-specific C(sp^3)-H deuteration of sulfonamides **1a–x**. Standard conditions: **1** (0.20 mmol), **2** (0.22 mmol) and AIBN (0.06 mmol) in $CHCl_3$ (1.0 mL) and D_2O (0.5 mL) were stirred at 85 °C for 24 h under argon atmosphere. Deuterium incorporation was determined by HR-MS (ESI) analysis. Yield of isolated product. [a] Performed on gram scale. [b] The free amine **3i'** was obtained by deprotection of the benzoyl group upon treatment with Tf_2O, 2-F-pyridine and *i*-BuMgBr in CH_2Cl_2 (see Supporting Information).

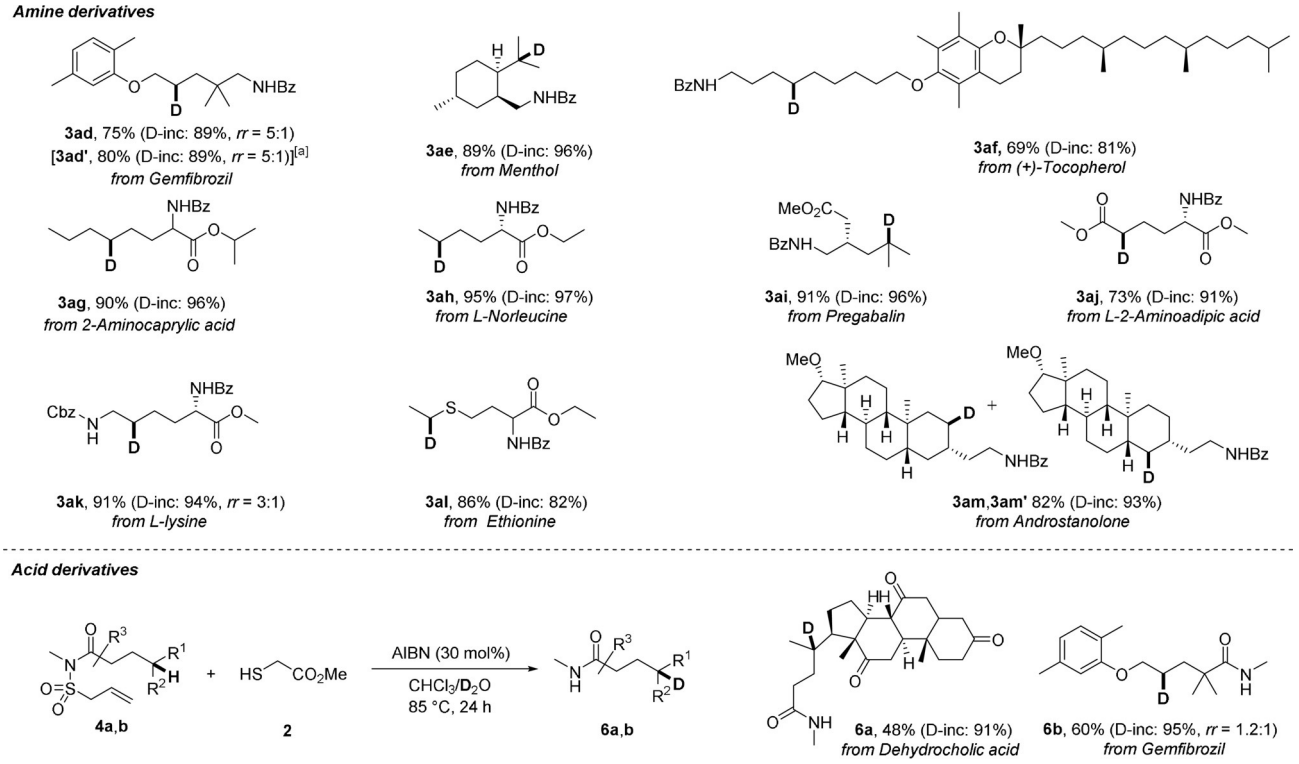
conditions (for details on reaction optimization, see the Supporting Information). Replacing $CHCl_3$ by the more expensive $CDCl_3$ did not further improve the D-content.

With the optimized conditions in hand, the substrate scope was investigated. The starting allylsulfonamides **1** were readily prepared from the corresponding amines (see Supporting Information). Different N-protecting groups (PG) were tested first and we found that replacing the benzoyl group by other typical PGs led to lower D-incorporation or yield (see **3a**–**3f**). Methine C–H deuteration worked efficiently for various systems including cyclic congeners to give the products **3g**–**3m** in good to excellent yields (80–92%) and high level of deuterium incorporation (81–97%). For all these cases, regioselectivity for deuteration was complete. When the reaction was performed on lager scale, a slight decrease of the yield and D-incorporation was noted (**3i**). Notably, the deuteration occurred fully site-selectively also for substrates that contain more than one tertiary C–H bond (**1g**, **1h**), documenting the advantage of the intramolecular HAT-strategy.

Along with tertiary C(sp^3)–H bonds, the more challenging deuteration of secondary C(sp^3)–H bonds was achieved by using this novel method (**3n**–**3y**). As expected, yields for deuteration and D-content of the less activated secondary C–H bonds were slightly lower, as compared to the methine deuteration. All these products were isolated with excellent regioselectivity and compounds **3q**–**3t** were formed as mixture of the two diastereoisomers. Due to signal overlap in the NMR, unambiguous determination of the selectivity was not possible. Moreover, the selective monodeuteration of benzylic positions was achieved (**3u**–**3y**, 66–77% yield; 84–94% D-inc). Substituents, such as Cl, Br, CF_3, OMe, in different positions of the aryl group are well tolerated, albeit the 2-chloro substituted congener led to a slightly decreased yield but with comparable D-incorporation (**3x**, 66% yield, 91% D-inc), demonstrating that steric factors play a role. As expected, the Thorpe–Ingold effect improves D-incorporation efficiency (**3v**–**3y**).

We next tested deuteration of primary C(sp^3)–H bonds, where the intramolecular 1,5-HAT is thermodynamically less favored. Not surprisingly, remote radical deuteration of the non-activated terminal methyl group in **1z** occurred in lower yield and lower D-incorporation (**3z**, 52% yield; 42% D-inc). However, sulfonamides **1aa**–**1ac** bearing an activating heteroatom at the γ-position, such as oxygen, sulfur or nitrogen, could be successfully deuterated at the methyl group to afford the deuterated products **3aa**–**3ac** in 67–83% yields with high levels of deuterium incorporation (86–93%).

Motivated by the broad scope of our method, we then tested its applicability to the site-selective deuteration of drug derivatives and biologically more relevant compounds starting with primary amines and carboxylic acids (Scheme 3). Introduction of a deuterium atom at the δ-position into amines derived from gemfibrozil (**3ad**) and menthol (**3ae**) was achieved in 75–89% yield with high D-incorporation (89–96%). For the gemfibrozil-derived substrate **1ad** bearing

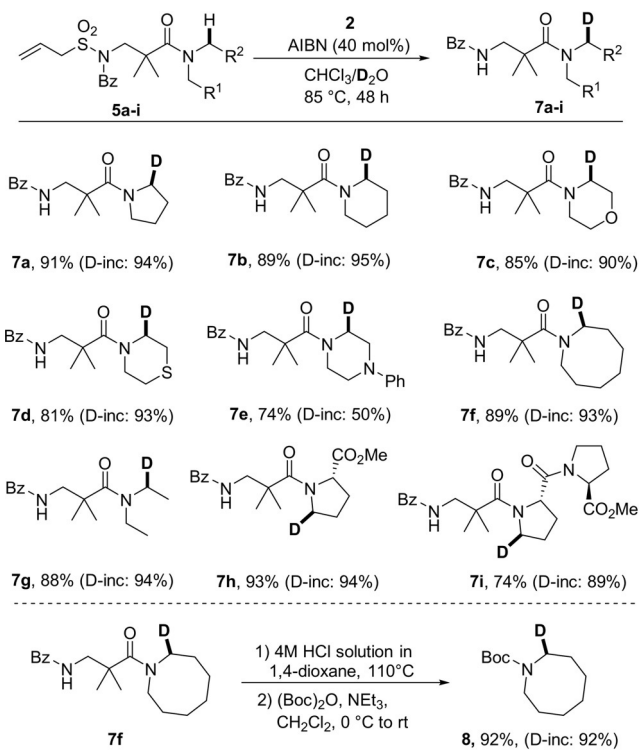


Scheme 3. Remote C(sp^3)-H deuteration of drugs and natural product derivatives starting with primary amines and carboxylic acids. Conditions: **1** and **4** (0.20 mmol), **2** (0.22 mmol), and AIBN (0.06 mmol) in $CHCl_3$ (1.0 mL) and D_2O (0.5 mL) were stirred at 85 °C for 24 h under argon atmosphere. The amount of deuterium incorporation was determined by HR-MS (ESI) analysis. Yield of isolated product for reaction run on a 0.2 mmol scale. [a] The free amine **3ad'** was obtained by deprotection of the benzoyl group upon treatment with Tf_2O, 2-F-pyridine and *i*-BuMgBr in CH_2Cl_2 (see Supporting Information).

a phenoxy substituent, the D-regioisomer formed via a 1,6-HAT was obtained as minor product (regioselectivity = 4:1). A (+)-tocopherol derivative that is conjugated with an 9-aminononyl chain via the phenolic O-atom was site-selectively deuterated with a good level of D-incorporation (see **3af**). Various amino acid esters derived from natural amino acids could be deuterium-labelled at their side chains via this strategy. Hence, sulfonamides prepared from 2-aminocaprylic acid, L-norleucine, pregabalin, L-2-aminoadipic acid, L-lysine and ethionine were converted with excellent yield and high D-incorporation to the corresponding D-derivatives **3ag**–**3al**. For the lysine-derivative **3ak**, a small amount of the regioisomeric product derived from a 1,6-HAT was observed. Deuteration occurred (if applicable) non-diastereoselectively for these amino acid esters. An androstanolone-derived steroid could be labelled to give the product in 82% yield and 93% D-incorporation as a mixture of the two regioisomers **3am** and **3am′**.[21] Notably, the benzoyl protecting group could be removed to give D-labelled free amines (see **3i′** in Scheme 2 and **3ad′** in Scheme 3).

We next investigated whether the remote site-selective deuteration also works on acid derivatives. To this end, the amides **4a** and **4b** were readily prepared by reacting the corresponding acid chlorides with N-methyl allylsulfonamide (see Supporting Information). Pleasingly, γ-C(sp^3)-H HIE reaction could be performed under the above optimized conditions on the steroid derivative **4a** carrying multiple stereogenic centers and tertiary C–H bonds to deliver the monodeuterated product **6a** as single regioisomer in 48% yield with high level of deuterium incorporation (91%, *dr* = 1.5:1). An amide derived from gemfibrozil also furnished deuterated products **6b** in good yields and high D-incorporation (95%) as a mixture of two regioisomers (1.2:1).

To further demonstrate the utility of the remote deuteration, we further expanded our method to the site-selective α-deuteration of secondary amines via an auxiliary aided remote HIE strategy. An easily removable β-alanine-based auxiliary was designed for accessing the desired site-selectively deuterated compounds via 1,6-HAT to N-radicals, which are generated from readily prepared N-allylsulfonamides **5** (Scheme 4). Under slightly modified reaction conditions, the targeted deuterium-labelled compounds **7** were obtained in excellent yields and high level of D-incorporation. Hence, pyrrolidine, piperidine, morpholine, thiomorpholine, piperazine, azocane and diethylamine, could be efficiently D-labelled at their α-position via this strategy (**7a**–**7g**). In these cases, D-incorporation level was high (> 90%). However, deuteration of the 1-phenylpiperazine-derived substrate **5e** gave the D-labelled product **7e** with moderate 50% D-incorporation (74% yield). Further, the L-proline methyl ester **5h** and the L-prolyl-L-proline dipeptide ester **5i** provided the corresponding α-D-labelled derivatives **7h**–**7i** in 74–93% yields with 89–94% deuterium incorporation. Due to signal overlap in the NMR, unambiguous determination of the diastereoselectivity was not possible. Importantly, we also demonstrated that the β-alanine-based auxiliary can be readily removed as documented by the hydrolysis of the D-labelled amide **7f** under acidic conditions to give after

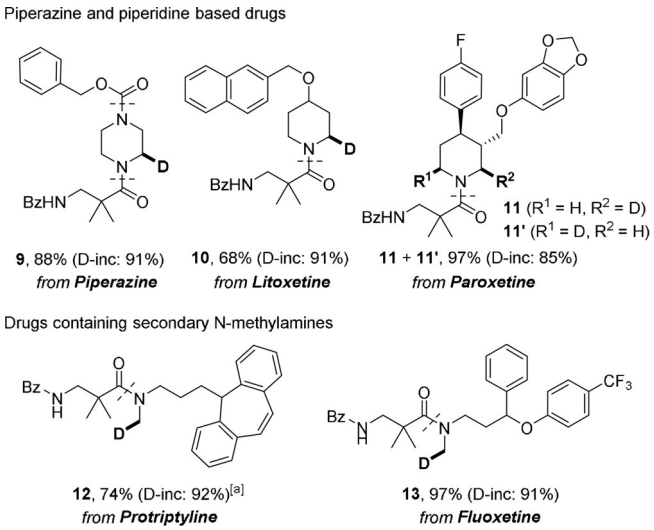


Scheme 4. Remote site-selective C(sp^3)-H deuteration of sulfonamides **5a–i**. Conditions: **6** (0.20 mmol), **2** (0.33 mmol) and AIBN (0.08 mmol) in $CHCl_3$ (1.0 mL) and D_2O (0.5 mL) were stirred at 85 °C for 48 h under argon atmosphere. Deuterium incorporation was determined by HR-MS (ESI) analysis. Yield of isolated product.

renewed N-protection the Boc-protected α-D-azocane **8** in 92% overall yield without compromising D-content (92%).

Next, we sought to explore the practicality of the site-selective α-deuteration of secondary amines by choosing commercially available drugs (Scheme 5). We found that for biologically active compounds containing the piperazine and piperidine scaffold, such as Piperazine (its citrate salt as anthelmintic), Litoxetine (antidepressant) and Paroxetine (antidepressant), the remote site-selective α-deuteration occurred in excellent yields and high level of deuterium incorporation (**9**–**11**, **11′**, 68–97% yield; 85–91% D-inc). Determination of the selectivity of the D-labelled Paroxetine derivative was not possible due to signal overlap in the NMR. The novel deuteration protocol was also applicable to acyclic secondary N-methylamine containing drugs, such as Protriptyline (antidepressant) and Fluoxetine (antidepressant). In both cases, HIE occurred efficiently with complete regioselectivity at the N-methyl position in high yield with an excellent degree of deuteration (**12**–**13**, 74–97% yield; 91–92% D-inc).

We tested whether our optimized reaction conditions are compatible with biomolecules to document the robustness of this transformation.[22] Deuteration of **1a** (0.2 mmol) to **3a** was conducted in the presence of an array of biomolecules, including natural amino acids, nucleic acids, and proteins. We found that upon addition of an unprotected biomolecule (1 equiv), such as L-cysteine, L-tyrosine, L-serine, L-methionine, guanosine, uridine, naringine, a DNA single strand



Scheme 5. Site-selective α-deuteration of drugs comprising a secondary amine moiety via remote HIE reaction. Conditions: allylsulfonamides (0.20 mmol), **2** (0.33 mmol) and AIBN (0.08 mmol) in $CHCl_3$ (1.0 mL) and D_2O (0.5 mL) were stirred at 85 °C for 48 h under argon atmosphere. Deuterium incorporation was determined by HR-MS (ESI) analysis. Yield of isolated product. [a] Performed on a 0.1 mmol scale.

(10 mg), and bovine serum albumin (10 mg), the remote C(sp^3)-H deuteration reaction proceeded smoothly with little or no impact on its synthetic efficiency (see Supporting Information). Only in the case of L-cysteine containing a thiyl group, the yield of **3a** dropped (47 %) but the D-incorporation level remained satisfactory (89 % D-inc). These experiments convincingly demonstrate that the process well accommodates various functional groups and biomolecules.[23]

Conclusion

In summary, we have developed a robust metal-free remote HIE reaction at various C(sp^3)–H bonds for δ-deuteration of primary amines, γ-deuteration of aliphatic acids and α-deuteration of secondary amines. For the α-deuteration of secondary amines, an easily removable β-alanine-based auxiliary is applied. With our developed method, various deuterium-labelled compounds are readily accessible, which are expected to have downstream applicability at serving as both mechanistic probes in chemistry and diagnostic tools in drug discovery research. The operationally simple and mild method allows for highly regioselective C–H deuteration mediated by intramolecular 1,5- or 1,6-HAT. Various unactivated and activated C(sp^3)–H bonds as well as primary C–H bonds next to heteroatoms can be site-selectively monodeuterated in good yields and with high D-incorporation. The scope of the method is broad, as documented by the successful monodeuteration of more complex compounds, including natural product derivatives and pharmaceutically relevant compounds, and the process tolerates a wide range of functional groups.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: deuteration · HIE method · pharmaceuticals · remote · site selectivity

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