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Ruthenium-Catalyzed Selective α,β-Deuteration of Bioactive Amines

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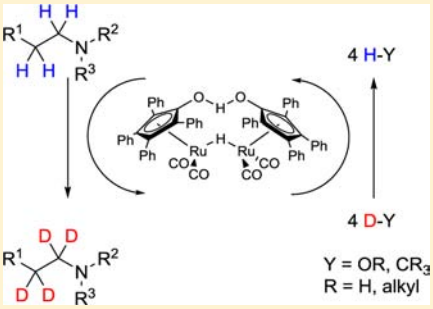
Supporting Information

ABSTRACT: A novel and convenient protocol for the catalytic hydrogen−deuterium exchange of biologically active tertiary amines utilizing the borrowing hydrogen methodology has been developed. In the presence of the readily available Shvo catalyst, excellent chemoselectivity toward α- and β-protons with respect to the nitrogen atom as well as high degree of deuterium incorporation and functional group tolerance is achieved. This allowed for the deuteration of complex pharmaceutically interesting substrates, including examples for actual marketed drug compounds. Notably, this method constitutes a powerful tool for the generation of valuable internal standard materials for LC−MS/MS analyses highly demanded for various life-science applications.



INTRODUCTION

The catalytic activation of aliphatic carbon−hydrogen bonds, recently referred to as "the unfunctional group" by Goldman and Goldberg[1] due to its omnipresence in nature and lack of reactivity, has been in the spotlight of research for several decades. As a result, numerous investigations toward selective C−C, C−N, or C−O bond formation utilizing the concept of C−H activation have been performed. In addition to these studies, also catalytic hydrogen deuterium exchange reactions (H/D-exchange) are of particular interest for both academic and industrial chemists.[2] Not only does this methodology provide a powerful tool for mechanistic investigations of a given organic[3] or organometallic reaction,[4] it also grants access to valuable deuterated compounds employed as functional materials, for instance, as optical polymer fibers for high-speed telecommunications systems,[5] or specifically labelled biomolecules for drug metabolism and toxicity studies.[6] Furthermore, the investigation of environmental, animal, and human samples by LC-coupled tandem MS analysis requires a steadily growing amount of suitable internal standards.[7] Showing virtually identical physical behavior whilst differing in molecular mass, deuterium labelled compounds are perfectly suited to fill this role and thus are more and more demanded for various life science applications. Because of the time-efficient post-synthetic introduction of deuterium into a given pharmaceutical target molecule, catalytic H/D-exchange reactions are clearly preferred over multi-step routes utilizing isotopically labelled building blocks. Unfortunately, many known labelling procedures do not precede chemo- and regioselectively or result in insufficient deuterium incorporation. As a result, mixtures containing various isotopomers and isotopologues of a single compound are formed.[8] On the other hand, a key prerequisite for the application of deuterated compounds as internal MS-standards in pharmaceutical applications is a narrow isotopologue distribution and sufficient mass difference as compared to the non-labelled compound.[9] Hence, the development of novel, selective, and efficient H/D-exchange methodologies constitutes an important and challenging task.

Among various methods already reported for catalytic H/D-exchange of aromatic and heteroaromatic protons,[10] at vinylic,[11] allylic,[12] and aliphatic positions,[13] and of C−H moieties adjacent to O- and N-based functional groups,[14] especially the latter are of particular interest for the generation of deuterium-labeled reference materials due to the ubiquitous occurrence of alkylamine scaffolds in biologically active compounds. So far, only few examples for H/D-exchange of amines using heterogeneous catalysts are known.[15] In general, deuteration with heterogeneous catalysts suffers from moderate deuterium incorporation[15a] and/or competitive labeling of aromatic C−H bonds.[15b,c] Because homogeneous transition metal catalysis is commonly considered to allow for more selective transformations, it is surprising that, apart from the pioneering work of Matsubara and co-workers covering primary amines[14c] and Lockley et al. dealing with secondary amines,[14d] homogeneously catalyzed deuteration of amines has been basically not investigated. To the best of our knowledge, examples for chemoselective catalytic H/D-exchange reactions of tertiary amine substructures in functionalized bioactive compounds have not been disclosed until to date.

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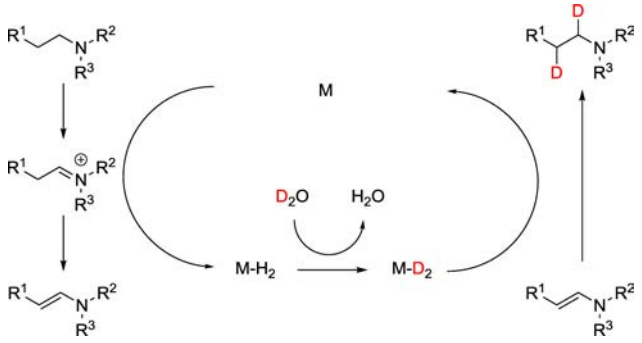
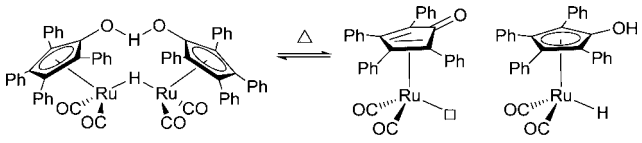
RESULTS AND DISCUSSION

On the basis of our ongoing interest in the development of methods for the synthesis of amines,[16] we had the idea to apply the so-called borrowing hydrogen methodology[17] also known as hydrogen autotransfer,[18] which represents a powerful concept for the activation of amines and alcohols, for the catalytic H/D-exchange of amines. Using tertiary amines as substrates, the key steps for this transformation include the generation of a reactive iminium cation or enamine intermediate followed by subsequent rehydrogenation. Obviously, an exchange of the abstracted hydrogen atom by deuterium in between both steps would result in the formation of the corresponding deuterated amine (Scheme 1).

Scheme 1. Borrowing Hydrogen Reaction Involving an H/D-Exchange Step



Although a variety of Ru- and Ir-based catalytic systems have been reported in borrowing hydrogen reactions, our recent success applying Shvo's catalyst[19,20] (Figure 1) in the activation of various primary, secondary, and tertiary amines implied using this versatile catalytic system as the starting point of our investigations.[21]

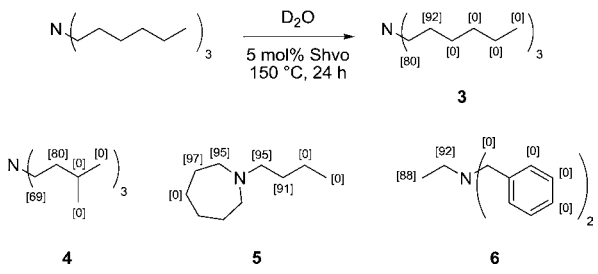


1 1a 1b

Figure 1. Shvo's catalyst in its dimeric (**1**), dehydrogenated (**1a**), and hydrogenated (**1b**) monomeric form.

Furthermore, deuteration experiments performed by the group of Casey[22] measuring kinetic isotope effects of hydrogen loss from **1b** indicated that rapid H/D-exchange of both protic and hydridic hydrogen atoms takes place in the presence of D_2O or deuterated alcohols. Indeed, preliminary experiments using trihexylamine as a model system showed that deuterium incorporation is achieved in a biphasic system comprised of D_2O and toluene in excellent yield. Assuming a mechanism similar to Scheme 1, involving an iminium-ion as intermediate, subsequent deuteration is supposed to yield the corresponding α-labeled trihexylamine only. However, NMR spectroscopic investigations of the product[23] revealed that deuterium incorporation occurred highly selectively in both α- and β-position to the nitrogen atom, indicating an enamine intermediate being formed within the course of the reaction. This trend was also observed for other trialkylamines investigated under analogue reaction conditions (Scheme 2).

Scheme 2. Regioselectivity of Deuterium Incorporation into Trialkylamines[a]



[a]Numbers in brackets indicate percentage of exchanged protons at the specified position determined by ^{1}H NMR.

Interestingly, no evidence for H/D-exchange at other positions of the alkyl chains is found, nor for benzylic protons in *N*-dibenzylethylamine (**6**). More precisely and on the basis of these observations, we propose a catalytic cycle similar to Scheme 3 involving coordination of the amine to **1a** in the first step, followed by abstraction of the acidic α-H atom by the cyclopentadienyl alkoxide moiety of **2a**. Coordination of the corresponding iminium-ion and subsequent β-hydride elimination yields the enamine as well as the hydrogenated Shvo monomer (**1b**).

In step 4, a Grotthuss-type mechanism[24] is responsible for the deuteration of the OH-proton of **1b** by the protic deuterated solvent, yielding species **1d**. H/D-exchange of the Ru−H moiety proceeding via an equilibrium between **1d** and **1f** over dihydrogen intermediate **1e**[22] will then furnish the deuterated Shvo monomer (**1c**). The corresponding back reaction of the first semicycle initiated by insertion of the enamine into the Ru−D bond of **1c** generates the desired α-,β-deuterated tertiary amine and **1a**, thus completing the catalytic cycle. It should be noted that the catalytic cycle shown above is proposed on the basis of detailed investigations of alkylation of amines with alcohols in the presence of the Shvo catalyst.[25] It is very likely that the activation of tertiary amines proceeds via a similar mechanism as compared to primary and secondary amines. Unfortunately, the corresponding intermediates could not be isolated or detected by spectroscopic investigations.

For an application as internal standards, deuterated substances need to be characterized by sufficient mass difference between the deuterated and the target compound as well as a narrow isotopologue distribution pattern to ensure signal overlapping of the respective MS signals is reduced to a minimum. Thus, given the already observed exclusive selectivity toward α- and β-protons, optimization experiments in terms of degree of deuterium incorporation monitored by mass spectrometry[26] were performed (Table 1). Raising the temperature above a critical threshold of 110 °C was required to observe significant catalytic activity. Further temperature increase afforded a considerably higher degree of deuteration up to an average of 10.2 D-atoms per molecule (Table 1, entry 3). Obviously, the comparatively high temperature and especially the long reaction time of 24 h disfavored the utilization of this methodology for more complex functionalized substrates. To our delight, these problems can be easily solved by switching from conventional heating to microwave irradiation, which allowed for similar performance at a much lower reaction time of 2 h. Not surprisingly, considering the equilibrium between the different reaction steps, increasing the amount of deuterium equivalents resulted in a greater degree of

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Scheme 3. Proposed Mechanism for the Shvo-Catalyzed Deuteration of Tertiary Amines Using *O*-Labelled Deuterium Sources

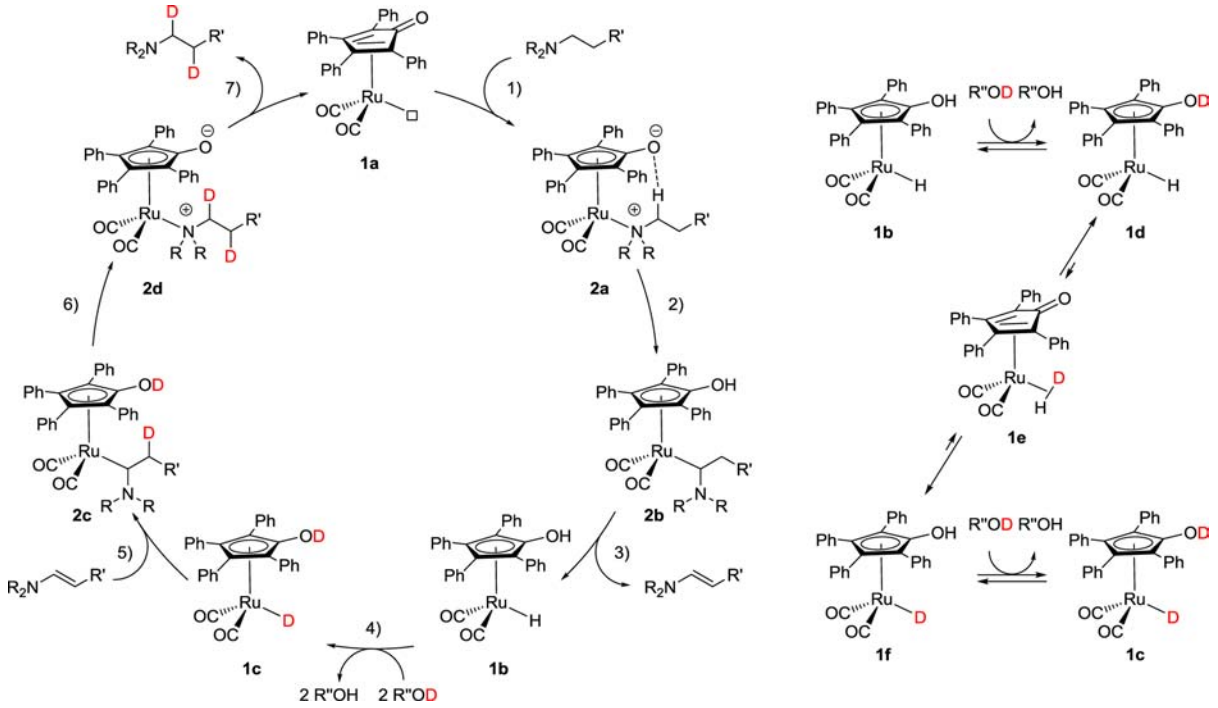
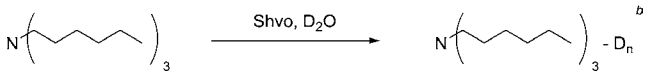


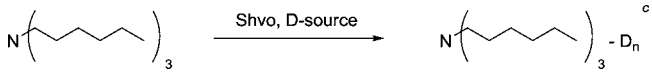
Table 1. Catalytic Deuteration of Trihexylamine: Investigation of Reaction Parameters[a]



entry	temp [°C]	Shvo [mol %]	time [h]	equiv of D_2O	D total[d]
1	110	2	24	150	4.9
2	130	2	24	150	6.3
3	150	2	24	150	10.2
4[c]	150	5	2	10	3.2
5[c]	150	5	2	50	7.0
6[c]	150	5	2	100	9.4
7[c]	150	5	2	500	11.0

[a]Reaction conditions: conventional heating, 0.5 mmol of trihexylamine, 2 mL of toluene. [b]*n* represents the number of incorporated deuterium atoms. [c]Reaction conditions: microwave irradiation (300 W max), 0.25 mmol of trihexylamine, 5 mol % Shvo, 1 mL of toluene. [d]Deuterium content determined by mass spectrometry.

Table 2. Catalytic Deuteration of Trihexylamine: Variation of Deuterium Sources[a]



entry	D-source	D total[d]	% D (α,β)[e]
1[b]	D_2O	9.4	78
2	CH_3OD	10.1	84
3	CD_3OD	10.7	87
4	CD_3OH	0.7	6
5	*t*-BuOD	9.8	82
6	$(CD_3)_2CDOD$	11.1	93
7	$(CH_3)_2CHOD$	4.4	37
8	acetone-d_6	3.2	27
9	cyclohexanone-d_{10}	8.6	72
10	TFA-d_1	0.0	0
11	toluene-d_8	0.0	0

[a]Reaction conditions: microwave irradiation (300 W max), 0.25 mmol of trihexylamine, 100 equiv of deuterium source, 5 mol % Shvo, 2 h. [b]1 mL of toluene was used as cosolvent to dissolve catalyst and substrate. [c]*n* represents the number of incorporated deuterium atoms. [d]Deuterium content determined by mass spectrometry. [e]Percentage of exchanged α-,β-protons.

deuteration of up to 11 D-atoms (Table 1, entries 4–7). On the basis of these results and the possibility to use process automation, we chose microwave heating as the standard procedure for the next investigations. As shown in Table 2, a variety of different deuterium sources are compatible with our catalytic system. For all *O*-deuterated alcohols utilized, experiments revealed two general trends: On the one hand, the examined deuterated solvents afforded good to excellent deuterium incorporation into trihexylamine without formation of side products. On the other hand, comparison of the observed values for isopropanol-d_1 and -d_8 (Table 2, entries 6 and 7), and to a lesser extent methanol-d_1, -d_3, and -d_4 (Table 2, entries 2–4), revealed that the exchanged deuterium atoms do not originate from the deuterated OH-function exclusively. This is not surprising considering the activation of deutero-alcohols under reaction conditions by **1a** forming the corresponding aldehyde or ketone and **1c**. Hence, dehydrogenation of isopropanol-d_8 yields two deuterium atoms per molecule rather than only one from isopropanol-d_1, explaining the lower degree of deuteration in the latter case. Interestingly, even acetone-d_6 and cyclohexanone-d_{10} can be successfully applied as deuterium sources (Table 2, entries 8 and 9). Apparently, partial enolization according to Scheme 4 of the ketone is responsible for this H/D-exchange at the α-position of alcohols or ketones, respectively. Strongly acidic deuteration reagents, as exemplified by TFA-d_1 (Table 2, entry 10), do not effect any observable H/D-exchange, presumably due to the formation of a less reactive ammonium salt. Finally, a control experiment ensured that toluene-d_8 (Table 2, entry 11), which

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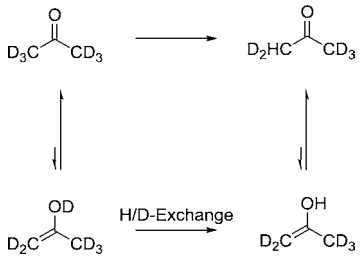
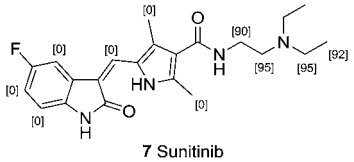
Scheme 4. Origin of Deuterium Equivalents from Acetone-d_6



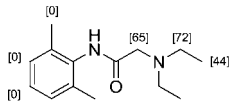
was utilized as cosolvent in preliminary studies to aid NMR-spectroscopic investigation, does not act as deuterium source itself.

To evaluate the substrate scope of our novel catalytic deuteration procedure, three currently marketed drugs featuring a trialkyl moiety were chosen as benchmark compounds (Scheme 5). We were pleased to find that in all

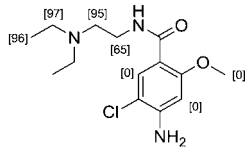
Scheme 5. H/D-Exchange of Actual Market Drug Compounds[a]



7 Sunitinib



8 Lidocaine



9 Metoclopramide

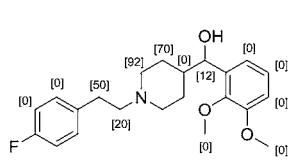
[a]Numbers in brackets indicate percentage of exchanged protons at the specified position determined by ^{1}H NMR.

cases highly selective H/D exchange with good to excellent degree of deuteration was achieved! Bearing various different functional groups, the ability to adjust the reaction conditions for each compound by choice of an adequate deuterium source proved to be of great importance to suppress unwanted side reactions. For example, utilization of isopropyl alcohol-d_8 allowed for satisfying results in the H/D-exchange of Lidocaine, a commonly used local anesthetic[27a] (**8**), although even raising the temperature to 170 °C did not result in complete deuteration at the expected positions. On the other hand, deuteration of Sunitinib, a multitargeted receptor tyrosine kinase inhibitor[27b] (**7**), and the antiemetic drug Metoclopramide[27c] (**9**) under analogous reaction conditions resulted in almost quantitative reduction of the double bond adjacent to the oxindole moiety of **7** and condensation with the aromatic NH_2-function of **9**, respectively. In these cases, inexpensive *tert*-butanol-d_1 can be easily used as substitute, circumventing the aforementioned side reactions due to its inability to be dehydrogenated to a corresponding ketone.

Notably, Lidocaine **8** as substrate gave a somewhat lower degree of deuteration (65−72% deuterium incorporation at the α-position) as compared to Sunitinib **7** and Metoclopramide **9**. We assume that the lower degree of deuterium incorporation into **8** is a result of the stable five-membered ring chelate, which can be formed only with this substrate.

Next, we examined the deuteration of compounds bearing typical bioactive motifs such as pyrrolidines, piperidines, and piperazines. Thus, four pharmaceutically interesting substrates were subjected to our catalytic system under optimized reaction conditions (Scheme 6). To our delight, efficient and fast H/D-

Scheme 6. H/D-Exchange of Pharmaceutically Interesting Compounds[a]



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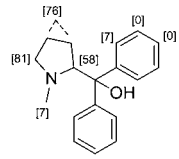

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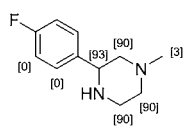

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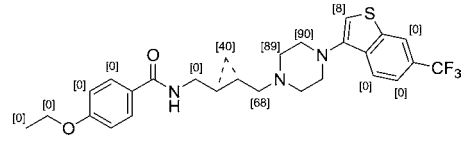

13

[a]Numbers in brackets indicate percentage of exchanged protons at the specified position determined by ^{1}H NMR.

exchange again predominantly in α- and β-positions to the nitrogen atoms was achieved. The resulting deuterated compounds are characterized by a narrow isotopologue distribution pattern and sufficient mass difference to the nondeuterated starting material (Table 3), underlining the capability to generate high-quality labeled reference material with the presented catalytic system. To the best of our knowledge, there exists no other methodology for similar deuteration of these functionalized molecules based on H/D-exchange.

In addition to α-,β-labeling, H/D-exchange of (2,3-dimethoxyphenyl)(1-(4-fluorophenethyl)piperidin-4-yl)-methanol (**10**) with isopropanol-d_8 also led to slight deuteration of the α-position in vicinity to the hydroxyl function. Taking the work of Bäckvall and co-workers on the Shvo-catalyzed racemization of benzylic alcohols[28] into consideration, this result is readily explained by partial oxidation and subsequent reduction of the OH-function. Clearly, H/D-exchange of the abstracted hydrogen in-between both steps is supposed to lead to the formation of the α-deuterated secondary alcohol. Noteworthy, selectivity toward methyl groups as present in (1-methylpyrrolidin-2-yl)-diphenylmethanol (**11**) and 3-(4-fluorophenyl)-1-methylpiperazine (**12**) was found to be much less pronounced. This observation is in accordance with our proposed mechanism, because the existence of β-hydrogen atoms appears to be essential for the activation of the amine. Thus, the slight H/D-exchange of *N*-methyl groups is assumed to proceed via an alternative mechanism, which is not clearly understood, yet. Deuteration of 4-ethoxy-*N*-(4-(4-(6-fluorobenzo-[*b*]thiophen-3-yl)piperazin-1-yl)butyl)benzamide (**13**) revealed that nucleophilicity of the nitrogen atom influences the reactivity toward H/D-exchange in a significant manner. While α- and β-protons adjacent to the piperazine moiety were readily exchanged, no deuteration next to the amide function occurred. In agreement

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Table 3. Composition of Isotopologue Mixtures from H/D-Exchange of Biologically Active Compounds 7−13[a]

			% $M_{(0+x)}$[e]															
entry	compd	D total[d]	M_0	M_{+1}	M_{+2}	M_{+3}	M_{+4}	M_{+5}	M_{+6}	M_{+7}	M_{+8}	M_{+9}	M_{+10}	M_{+11}	M_{+12}	M_{+13}	M_{+14}	M_{+15}	M_{+16}
1	7	13.7	0	0	0	0	0	0	0	0	0	0	0	3	9	18	39	24	7
2[b]	8	6.3	0	0	0	0	4	15	30	27	16	3	0	0	0	0	0	0	0
3[c]	9	13.0	0	0	0	0	0	0	0	0	0	0	0	5	20	31	23	13	6
4	10	10.0	0	0	0	0	0	0	0	0	9	14	30	23	15	4	0	0	0
5	11	5.9	0	0	0	1	6	22	36	29	5	0	0	0	0	0	0	0	0
6	12	6.5	0	0	0	0	4	4	20	50	14	3	0	0	0	0	0	0	0
7	13	10.5	0	0	0	0	0	0	0	0	0	6	18	35	27	9	2	0	0

[a]Reaction conditions: microwave irradiation (300 W max), 150 °C, 0.25 mmol of amine, 10 mol % Shvo. [b]Reaction was run at 170 °C. [c]1 mL of toluene was used as cosolvent to dissolve catalyst and substrate. [d]Incorporated deuterium atoms per molecule as average over all isotopologues determined by ESI mass spectrometry. [e]Relative amount of the undeuterated (M_0) and deuterated ($M_{(0+x)}$) isotopologues in the product isotopologue mixture in percent.

with this observation, electron-deficient ammonium salts, in particular **12** hydrochloride and **13** ammonium acetate, gave virtually no deuterium incorporation. Preparation of the corresponding free bases[29] prior to H/D-exchange is therefore essential for selective and sufficient deuteration in these cases.

SUMMARY

In conclusion, we developed a novel α-,β-H/D-exchange procedure for amines utilizing the so-called borrowing hydrogen methodology. Reactions with a wide range of deuterated solvents are conveniently carried out either thermally or by using microwave technology in the presence of the commercially available Shvo catalyst. The preferred protocol for the catalytic deuteration of amines makes use of microwave heating in the presence of 5−10 mol % Shvo catalyst. This procedure ensures high deuterium incorporation into the target compound with outstanding regioselectivity. Applying the right choice of deuterium source, the methodology shows broad substrate scope. As a rule of thumb, utilization of isopropyl alcohol-d_8 is recommended for most substrates, but especially for compounds bearing primary and secondary OH-groups to avoid inadvertent oxidation to the respective ketones. Conversely, substrates comprising functional groups prone to hydrogenation under the given reaction conditions, for example, ketones or olefinic double bonds, require the use of nonreductive deuteration reagents, such as *tert*-butanol-d_1. While aromatic amines, such as compound **9**, can be selectively deuterated, the presence of primary aliphatic amines leads to side reactions and represents an actual limitation of the methodology. In the latter case, dehydrogenation to the corresponding imine leads to borrowing hydrogen-type dimerization or transalkylation reactions. However, application of suitable protection groups, for example, benzyl (Scheme 2, compound **6**), permits the deuteration of these compounds, too. While most transition metal-catalyzed CH/D-exchange reactions are performed only with relatively simple model substrates, the present methodology allows for isotope labeling of "real" pharmaceuticals and bears great potential for the production of labeled LC−MS/MS reference materials. Noteworthy, the ability to perform highly selective H/D-exchange of α- and β-*N*-alkyl protons, which constitute positions of metabolic attack for many biologically active compounds, might be of interest for the development of new drug entities utilizing kinetic isotope effects to enhance crucial pharmacokinetic properties.[30]

ASSOCIATED CONTENT

Supporting Information

General experimental procedures, compound characterization, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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