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Stereoretentive Deuteration of α-Chiral Amines with D_2O

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Supporting Information

ABSTRACT: We present the direct and stereoretentive deuteration of primary amines using Ru-bMepi (bMepi = 1,3-(6′-methyl-2′-pyridylimino)isoindolate) complexes and D_2O. High deuterium incorporation occurs at the α-carbon (70−99%). For α-chiral amines, complete retention of stereochemistry is achieved when using an electron-deficient Ru catalyst. The retention of enantiomeric purity is attributed to a high binding affinity of an imine intermediate with ruthenium, as well as to a fast H/D exchange relative to ligand dissociation.

Deuterium- and tritium-labeled compounds are widely applied in the pharmaceutical industry to enhance the pharmacokinetic properties of a drug, as metabolic tracers, and as mass spectrometry standards.[1] For drug development, D/T labeling offers a powerful approach for further modifications based on the known characteristics of the protio molecule. As a result of the kinetic isotope effect, the C−D bond is more inert toward metabolic oxidation compared with the C−H isotopologue. Thus, improvements in pharmaceutical residence times can be achieved at low cost and with predictable outcomes.[1a] Since this concept was first applied to bioactive molecules,[2] a substantial effort has been devoted to prepare and patent deuterium-labeled pharmaceuticals.[1e,3] However, labeled compounds are commonly prepared via multistep syntheses and require expensive labeled starting materials. As an alternative strategy, isotope exchange through C−H bond activation allows direct labeling and ideally may be used as a late-stage modification of a complex molecule.[4]

The primary amine unit is an important functional group found in a variety of pharmaceutical drugs and is commonly metabolized through oxidative deamination by amine oxidase enzymes.[5] For such compounds, the *in vivo* efficacy can be significantly improved by deuterium incorporation at a C−H bond that is adjacent to the primary amine nitrogen atom. For example, the bioactive compounds tryptamine,[2] amphetamine,[6] and dopamine[7] have been targeted for deuterium incorporation at the α-C−H position to slow metabolic oxidation (Figure 1). However, the labeling protocols for these compounds require multistep syntheses, resolution techniques for α-chiral amines, and/or use expensive labeled starting materials.[6−8]

A promising alternative strategy to incorporate deuterium into the amine unit is to employ catalytic hydrogen transfer using a ruthenium catalyst in D_2O.[9,10] This approach exploits reversible dehydrogenation/hydrogenation coupled with H/D exchange processes. However, the direct labeling of primary amines in this manner faces major challenges. (De)-hydrogenation catalysts often facilitate transamination in the presence of primary amines, leading to a mixture of products.[9a,11] Furthermore, many bioactive compounds contain α-chiral amines, which can racemize through a prochiral imine intermediate during reversible β-hydride elimination.[12,13] Finally, D_2 is commonly employed as the deuterium source, which is more expensive than D_2O and imposes additional operational challenges.[14] To overcome these limitations, we present a stereoretentive protocol for labeling primary amines that employs inexpensive D_2O.

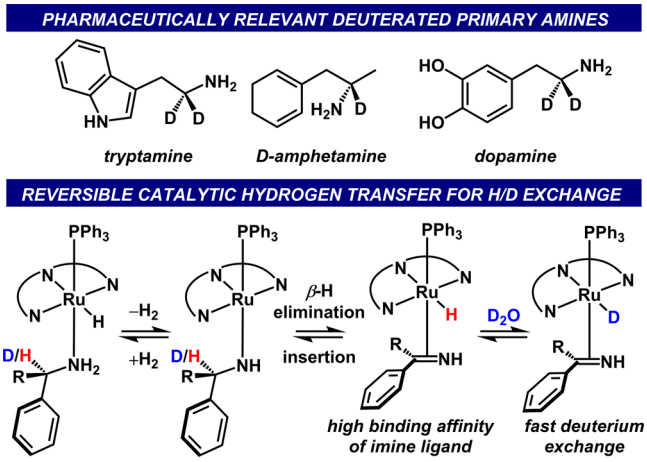

Figure 1. Select deuterated bioactive primary amines (top). Conceptual development of stereoretentive H/D exchange using hydrogen transfer (bottom).

We recently reported a series of Ru-bMepi complexes (bMepi = 1,3-(6′-methyl-2′-pyridylimino)isoindolate) that are excellent alcohol and amine dehydrogenation catalysts.[15] For amine dehydrogenation, imine intermediates remain coordinated to Ru following reversible β-hydride elimination from a Ru−amido intermediate (Figure 1).[16] This high binding affinity avoids the more commonly observed transamination reaction.[11] Due to the higher binding affinity of the imine vs the amine, we hypothesized that a chiral amine would retain its stereochemistry during a reversible β-hydride elimination process. This affinity could be exploited for stereoretentive deuteration if H/D exchange with the Ru−H occurs faster than reversible amine dehydrogenation.

To evaluate whether chiral amines retain their stereochemistry during the H/D exchange reaction, we selected (*S*)-1-phenylethylamine (**7**, Figure 2) as our model substrate. Notably, **7** is used as an advanced building block for syntheses

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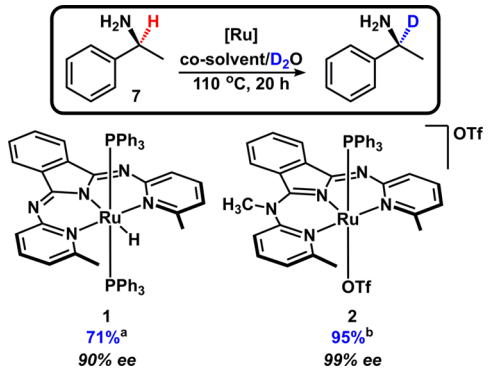


Figure 2. Stereoretentive deuterium incorporation of (*S*)-1-phenylethylamine with **1** and **2**. [a]1 mol % **1** in methylcyclohexane. [b]2 mol % **2** in Me-THF.

of more complex molecules and is commercially available.[17] In a sealed vessel containing 1.24 mmol of (*S*)-1-phenylethylamine, 1 mol% **1**, and a 15:85 ratio of methylcyclohexane to D_2O, 71% deuterium incorporation was observed into the α-C−H position.[18] Significantly, H/D exchange proceeded with 90% ee.

The preservation of the stereochemistry in **7** is atypical in the absence of a chiral ligand.[19] Thus, we propose that two key factors influence stereoretention with **1**: (1) H/D exchange on ruthenium is fast in comparison to ligand (imine) exchange, and (2) the binding affinity of the imine intermediate is directly related to the retention of configuration for (*S*)-1-phenylethylamine. The Ru−H/Ru−D exchange reaction was evaluated using **1** by adding 3 equiv of D_2O to a solution of **1** in THF-d_8.[20] The appearance of HOD and H_2O after 10 min confirmed exchange of the Ru−H with D_2O. In contrast to amine dehydrogenation by **1**, which requires at least 100 °C,[16] the H/D exchange of **1** with D_2O occurred at 35 °C. The facile exchange at low temperatures suggests that H/D scrambling of the Ru−H bond is much faster than amine dehydrogenation.[21]

To further mitigate racemization of chiral amine substrates, a more electrophilic Ru catalyst was selected to limit dissociation of the prochiral imine intermediate. The cationic complex $Ru(bMepi^{Me})(PPh_3)(OTf)_2$ (**2**, Figure 2)[22] was hypothesized to have a higher binding affinity for the imine ligand and, by extension, higher stereoretention compared to **1**. Optimal conditions were obtained by using a 15:85 ratio of 2-methyltetrahydrofuran (Me-THF) to D_2O in a sealed 3 mL tube,[23] with 2 mol% **2** for 20 h, which resulted in 95% deuterium incorporation with *complete retention of stereochemistry* (Figure 2).

Based on the limited number of amine deuteration procedures,[9,10,14] we applied our optimized conditions to a variety of chiral and achiral primary amines. For all substrates, high deuterium incorporation was identified at the α-carbon (Figure 3).[18] Notably, the presence of electron-withdrawing or -donating substituents on the substrate did not have a negative impact on the deuterium incorporation or enantiomeric purity. Substrates **8** and **9**, which contain *para*-methoxy and *para*-chloro substituents, proceeded with complete retention of stereochemistry and 99 and 88% incorporation of deuterium, respectively. Deuterated bioactive compounds, such as dopamine (**11**),[7] tryptamine (**12**),[2] and D-amphetamine (**13**),[6] as well as precursors to bioactive compounds (**10**, **14**, **15**),[24] were obtained using our methodology. Importantly, a simple acidic workup removed the ruthenium catalyst, **2**. For

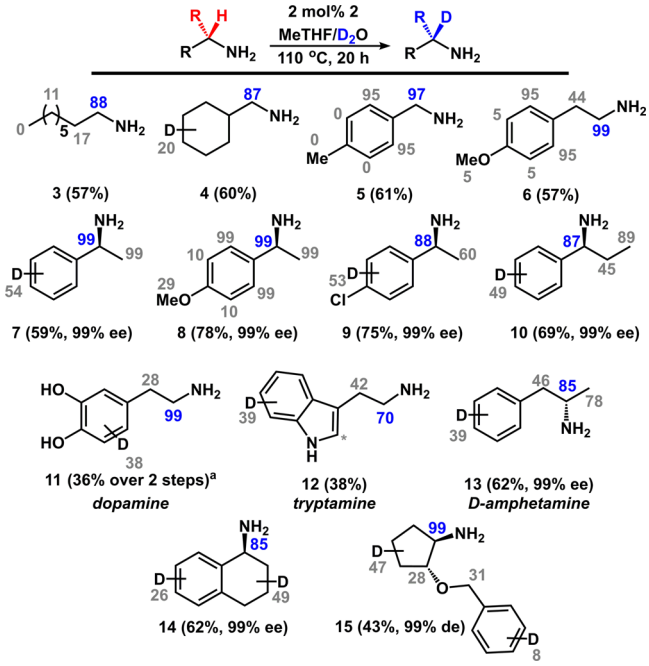
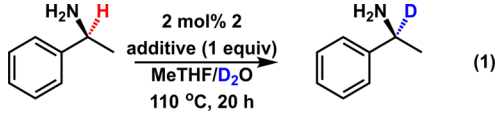


Figure 3. Deuteration of primary amines with **2** and D_2O. Deuterium incorporation was determined by ^2H NMR spectroscopy. Percent recovery shown in parentheses. [a]Formed from the deprotection of 3,4-dimethoxyphenylethylamine.

example, <4 ppm Ru was detected by ICP-OES after the isolation of the ammonium chloride salt of 4-methoxy-2-phenethylamine (**6**). The convenient workup and low level of Ru further highlights the potential to employ Ru-bMepi complexes for pharmaceutical applications.[25] The simple protocol for deuteration, coupled with the high deuterium incorporation, product recovery, and low residual metal content, demonstrates the broad utility of this catalytic deuteration method.

Many pharmaceutically relevant chiral amines contain heterocycles, amide, and ester functional groups. Such functional groups may erode the enantiomeric purity by competitive coordination during reversible hydrogen transfer. To evaluate this possibility, we examined the functional group tolerance and stereoretention of **7** in the presence of several common functional groups (Table 1).[26] In the presence of other *L*-type donor ligands, such as 2-butylthiophene (entry 1) and 3,5-lutidine (entry 2), the deuterium incorporation decreased to

Table 1. Deuteration of (*S*)-1-Phenylethylamine in the Presence of Common Functional Group Additives[a]



entry	additive	% D	% ee
1	2-butylthiophene	55	99
2	3,5-lutidine	24	99
3	methyl benzoate	85	99
4	*N*-methyl-*N*-phenylacetamide	95	99
5	2-vinylnaphthalene	0	N/A

[a]Deuterium incorporation was determined by ^2H NMR spectroscopy using acetonitrile-d_3 as an internal standard

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55% and 24%; however, the enantiomeric purity was retained. Notably, additives such as esters and amides did not decrease deuterium incorporation or enantiomeric purity (entries 3 and 4). One limitation, however, is the incompatibility with hydrogen acceptors such as 2-vinylnaphthalene (entry 5). The proposed mechanism for deuterium incorporation relies on a reversible hydrogen transfer process (Figure 1); hence, an additive that irreversibly removes hydrogen, such as an alkene, prevents deuterium incorporation. Overall, these results highlight the potential and limitations of Ru-bMepi complexes as late-stage stereoretentive deuteration catalysts with D_2O.

The high binding affinity of the imine intermediate is proposed to be crucial to the stereoretention. This hypothesis was evaluated by comparing the dissociation energies of prochiral imine with analogous ketone intermediates (derived from alcohol precursors). Although the dissociation energy of benzaldimine is endergonic by 8.2 kcal/mol, acetophenone dissociation is exergonic by −3.9 kcal/mol (Figure 4).[16,27]

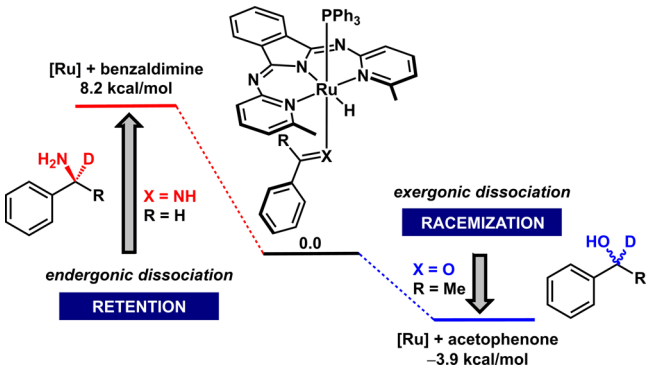


Figure 4. Comparison of the binding affinity of alcohols and amines and the effect on stereoretention.[27]

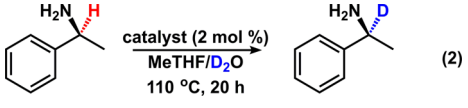
Consistent with these data, when (*S*)-1-phenylethanol was subjected to conditions for H/D exchange, complete racemization was observed. The requirement for a coordinated imine intermediate is further supported by comparison with the known outer-sphere catalyst, Shvo's complex ($[(\eta^5\text{-}Ph_4C_4CO)_2H]Ru_2(CO)_4(\mu\text{-}H)$).[13a,d] We hypothesized that the % ee may erode with catalysts that operate through an outer-sphere mechanism due to face-to-face exchange of the imine π-bond. Accordingly, a reduction in % ee was observed with Shvo's catalyst, providing deuterium incorporation of 78% with 50% ee (Table 2, entry 2).

Although an imine-bound intermediate appears to be a requirement for stereoretentive deuteration with **1** and **2**, we propose additional features of the Ru-bMepi catalyst system that enable this transformation: (1) a reversible β-hydride elimination step, (2) a faster H/D exchange process on ruthenium than ligand exchange of the imine (*vide supra*), and (3) limited rotation of the α-chiral amine, which may be facilitated by *ortho*-CH_3 groups in complexes **1** and **2**. To assess the first point, we examined the iridium pincer complex $[C_6H_3\text{-}2,6\text{-}(OP^tBu_2)_2]IrH_2$. This complex is one of the few reported catalysts in addition to **1** that facilitates the double dehydrogenation of primary amines.[15c,28] However, the mechanism is distinct from **1**. Amine dehydrogenation by **1** occurs via a rate-determining hydride protonation step followed by fast and reversible β-hydride elimination of a Ru−amido species.[16] In contrast, $[C_6H_3\text{-}2,6\text{-}(OP^tBu_2)_2]IrH_2$ facilitates a reversible N−H bond oxidative addition followed by *irreversible* β-hydride elimination.[28a] When $[C_6H_3\text{-}2,6\text{-}(OP^tBu_2)_2]IrHCl$ was subjected to H/D exchange conditions,[29] deuterium incorporation of (*S*)-1-phenylethylamine provided only 7% deuterium incorporation (Table 2, entry 3).

The *ortho*-CH_3 groups may also contribute to high stereo retention by limiting rotation around the Ru−imine bond. Thus, we examined known inner-sphere (de)hydrogenation catalysts that have reported imine-bound ruthenium intermediates yet lack significant steric bulk around the ruthenium center (Table 2). The ruthenium catalyst $Ru(PCy_3)_2(H)_2\text{-}(H_2)_2$[30] facilitates amine double dehydrogenation of 1-octylamine to 1-octanenitrile,[31] suggesting that this catalytic system may also promote H/D exchange with high enantiomeric purity. However, under our optimized conditions, we observed 61% deuterium incorporation into (*S*)-1-phenylethylamine, with only 65% ee (entry 4). Similarly, the inner-sphere catalyst $RuCl_2(PPh_3)_3$ resulted in 94% deuterium incorporation but only 68% ee (entry 5). These studies suggest that catalysts **1** and **2** have an additional feature that enables the retention of enantiomeric purity. We propose that the *ortho*-CH_3 substituents contribute to the high enantiomeric excess by preventing rotation of the α-chiral amine when coordinated to complexes **1** and **2**.[32] Our analysis of known (de)hydrogenation catalysts highlights the unique role of the bMepi ligand. In the absence of chiral ligands, stereoretentive hydrogen transfers are not common.[14] We have identified the key features of Ru-bMepi complexes that enable stereoretention.

Limited examples of primary amine deuteration through C−H bond activation have been reported,[10] and even fewer exist for α-chiral amines.[14] Our study provides a new strategy to use an achiral hydrogen transfer catalyst for the stereoretentive H/D exchange of α-chiral amines—the first homogeneous catalyst to promote this transformation. We found that the highest stereoretention is achieved with a catalyst that tightly coordinates a prochiral imine intermediate, facilitates reversible β-hydride elimination, and fast Ru−H/Ru−D exchange. Overall, these studies provide a new method for stereoretentive C−H activation and will likely find application for late-stage deuteration as well as synthetic methodology.

Table 2. Deuteration of (*S*)-1-Phenylethylamine with Known Hydrogen Transfer Catalysts



(2)

entry	catalyst	% D	% ee
1	**2**	95	99
2	$[(\eta^5\text{-}Ph_4C_4CO)_2H]Ru_2(CO)_4(\mu\text{-}H)$	78	50
3[a]	$[C_6H_3\text{-}2,6\text{-}(OP^tBu_2)_2]IrHCl$	7	N/A
4	$Ru(PCy_3)_2(H)_2(H_2)_2$	61	65
5	$RuCl_2(PPh_3)_3$	94	68

[a]10 mol% NaO^tBu added.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b07879.

Experimental details and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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(32) $Ru(bpi)(Cl)(PPh_3)_2$ is *inactive* for amine dehydrogenation as well as H/D exchange. See ref 16 for more details.

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