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Selective α-Deuteration of Amines and Amino Acids Using D_2O

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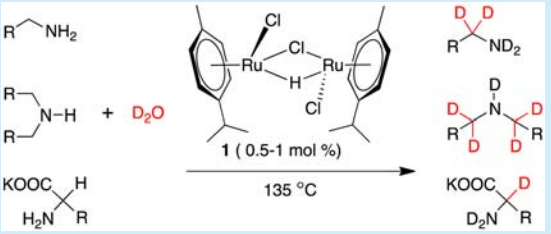
Supporting Information

ABSTRACT: Monohydrido-bridged ruthenium complex [{(η^6-*p*-cymene)RuCl}$_2$(μ-H-μ-Cl)] catalyzes (catalyst load: 0.5−1 mol %) α-selective deuteration of primary and secondary amines, amino acids, and drug molecules using deuterium oxide (D_2O) as a deuterium source. Mechanistic investigations revealed N−H activation of amines, which was also established by single-crystal X-ray analysis of an intermediate. β-Hydride elimination on amide ligand results in formation of imine-ligated ruthenium intermediate and subsequent 1,3-deuteride migrations to imine ligand leading to the selective deuteration at the α-CH_2 protons of amine functionality is proposed.



Selective deuteration of organic compounds is one of the important transformations in chemical synthesis, as deuterated organic compounds find widespread applications as NMR solvents, mechanistic probe in chemical and biological processes, biologically active compounds, and pharmaceuticals.[1] Deuterated organic compounds are uniquely suited as internal standards for quantitative LC-MS/MS analysis of life science samples.[2] Organic light-emitting diodes and optical fibers for high-speed telecommunication systems are also derived from them.[3] Deuteration of the reactive site repressed the undesired reaction pathways due to a kinetic isotopic effect, which was assimilated in the total synthesis of norzoanthamine.[4] When the metabolism of drugs involves cleavage of C−H bonds, deuteration of those covalently bound hydrogen atoms can provide an improved metabolomics profile and prevent formation of toxic metabolites.[5] Isotopically labeled drug candidates play a crucial role in understanding the metabolic profile of drug molecules and their toxicity assessment.[6] Thus, direct catalytic deuteration of these target molecules by C−H activation[7] is a highly desired protocol. From this perspective, deuteration of amines and amino acids gains significant importance, as around 92% of the drug candidates are nitrogen-containing compounds.

Rhodium and ruthenium catalysts are well explored for the synthesis of deuterated amines.[8] However, catalytic methods reported for the deuteration of primary and secondary amines essentially employ very limited high molecular weight non-functionalized amines and suffer from harsh reaction conditions, low labeling, and poor selectivity.[9] Ruthenium-catalyzed deuteration of primary and secondary amines was reported to occur under a high-pressure setup (3 mol % of catalyst, 150 °C, and 10 atm).[9a] Deuteration of secondary amines using a high load of ruthenium complexes (33.33 mol %, 150 °C) in DMSO-d_6/D_2O (5:1) medium together with DMF as cosolvent was also reported.[9b] Selective α,β-deuteration of tertiary amines was achieved by using Shvo's catalyst (5−10 mol %, 150 °C).[10] Recently, polymer-supported ruthenium nanoparticle catalyzed α-deuteration of amines[11] using deuterium gas (1−2 bar D_2) as a deuterium source was revealed in which only 40% deuteration occurred on primary amines.

α-Selective deuteration of amino acids remains a challenge, and it has been scarcely studied.[1,12] Sajiki and co-workers reported a heterogeneous Pd/C−H_2/D_2O catalytic system that required prolonged heating at high temperature (160 °C, 48 h) for the moderate deuteration at the α-position of 1-phenylalanine.[13] α-Deuterated glycine and its derivatives are often synthesized in multistep synthetic procedures (up to 9 synthetic steps) involving imine formation[14] or bislactim ether formation.[15] Recently, we reported the ruthenium pincer complex catalyzed selective deuteration of alcohols and terminal alkynes.[16] Herein, we report a monohydrido-bridged dinuclear complex [{(η^6-*p*-cymene)RuCl}$_2$(μ-H-μ-Cl)] (**1**) catalyzed[17] facile selective α-deuteration of amines and amino acids using deuterium oxide as a deuterium source.

At the outset, we performed the deuteration of benzylamine using complex **1** (0.5 mol %) in D_2O (0.4 mL) at 135 °C for 24 h and found excellent deuterium incorporation (95%) at sp^3-α-CH_2 protons. Reducing the catalyst load to 0.2 mol % led to the partial deuterium incorporation (55%). Thus, an assortment of primary amines was subjected to this catalytic deuteration using 0.5 mol % of **1**, which resulted in efficient deuteration at their α-CH_2 positions. Arylmethylamines (entries 1−3, Table 1), 2-picolylamine, and 3-picolylamine provided facile deuteration at the α-CH_2 position (entries 4 and 5), despite the fact that 2-picolylamine is well known for it's coordination ability with ruthenium.[18] A series of linear aliphatic amines displayed facile deuteration selectively at α-CH_2 (entries 6−13). When cyclohexylmethylamine and cyclohexylamine were reacted (entries 14 and 15), 77% and 70% deuteration were obtained, respectively, in their α-CH_2 positions. Octane-1,8-diamine exhibited efficient deuteration at both α-CH_2 positions. Notably, no detectable

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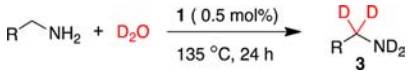
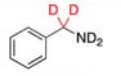
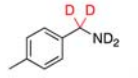
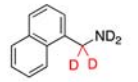
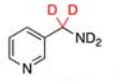
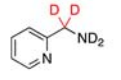
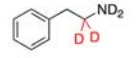
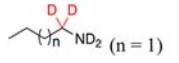
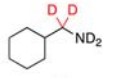
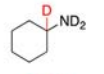
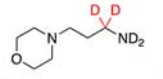
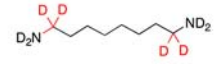
Table 1. Selective α-Deuteration of Primary Amines[a]



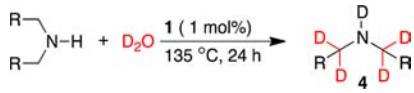
entry	product		deuteration (%)[b]	D_n[c]
1		**3a**	95	1.9
2		**3b**	75	1.5
3		**3c**	81	1.62
4		**3d**	95	1.9
5		**3e**	95	1.9
6[d]		**3f**	80:4	1.68
7	 (n = 1)	**3g**	57	1.14
8[d]	(n = 2)	**3h**	90:9	1.98
9[d]	(n = 3)	**3i**	91:6	1.94
10[d]	(n = 4)	**3j**	92:2	1.88
11	(n = 5)	**3k**	91	1.82
12	(n = 9)	**3l**	80	1.6
13	(n = 15)	**3m**	91	1.82
14		**3n**	77	1.54
15[e]		**3o**	70	0.7
16[f]		**3p**	85	1.7
17[g,h]		**3q**	81	3.24

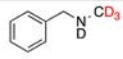
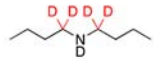
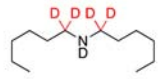
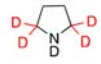
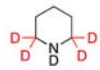
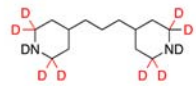
[a]Primary amine (0.5 mmol), catalyst **1** (0.0025 mmol, 0.5 mol %), and D_2O (0.4 mL, 20 mmol) were charged in a scintillation vial and heated to 135 °C. [b]Calculated from the integration of residual signals in ^1H NMR spectra. Maximum theoretical % of deuteration was 95.23%. [c]Average number of catalytically exchanged deuterium atoms per molecule (excluding the labile heteroatom-H protons). [d]Minor amount (2−9%) of β-deuteration also occurred. [e]Maximum theoretical % deuterium incorporation was 96.38%. [f]Reaction was carried out at 150 °C. [g]1 mol % of catalyst **1** was used. [h]Maximum theoretical % deuterium incorporation was 90.90%.

deuteration at β-CH_2 position is observed in these acyclic amines and diamines (entries 11−17, Table 1).

Secondary amines were tested in catalytic selective deuteration using 1 mol % of **1** (Table 2). Interestingly, when *N*-methyl-*N*-benzylmethylamine was subjected to catalysis, deuteration occurred only at *N*-methyl protons. Surprisingly, N-benzylic "CH_2" protons remained unaffected (entry 1, Table 2). Dibutylamine showed 71% deuterium incorporation (entry 2). When dihexylamine and cyclic secondary amines were examined, efficient deuteration at both α-positions occurred and provided products with high D content (D_n: 3.0−6.8) (entries 3−6).

Table 2. Selective α-Deuteration of Secondary Amines[a]



entry	product		deuteration (%)[b]	D_n[c]
1[d]		**4a**	95	2.85
2[e]		**4b**	71	2.84
3[e,f]		**4c**	89	3.56
4[e,f]		**4d**	75	3.0
5[e]		**4e**	79	3.16
6[f,g]		**4f**	85	6.8
7[f,g,h]		**4g**	83	6.64

[a−c]As shown in the footnote of Table 1 (catalyst **1** (0.005 mmol, 1 mol %) is used). Maximum theoretical % of deuteration. [d]95.23%. [e]94.11%. [f]88.88%. [g]0.01 mmol of **1** was used. [h]Reaction was carried out at 150 °C. 1,4-Dioxane (80 μL) was used as internal standard.

Piperazine was deuterated over all α-CH_2 positions (entry 7, Table 2). Unlike Shvo's catalyst, complex **1** was not effective in deuteration of tertiary amines, indicating different reactivity.[10]

As complex **1** turned out to be the most efficient catalyst for the selective α-deuteration of primary and secondary amines, we further envisaged expanding its scope to the labeling of biologically active molecules and amino acids. When L-phenylalanine was tested no significant deuterium incorporation was observed, perhaps attributable to the dilapidation of Ru hydride catalyst **1** in the presence of carboxylic acid functionality. To circumvent this setback, reactions were carried out with the potassium salt of L-phenylalanine (preneutralized with 1 equiv of KOH), and 84% α-deuteration was observed (entry 1, Table 3). The control experiment carried out with base (1 equiv) and without catalyst led to only 17% deuteration (entry 2). A series of proteinogenic, highly useful essential amino acids[19] were subjected to catalysis by **1** using deuterium oxide. Tyrosine exhibited only 40% deuteration due to low solubility (entry 3). Glycine exhibited 89% α-deuterium incorporation (entry 4). Alanine also showed 71% deuterium incorporation (entry 5). Hydroxy functionality containing serine showed facile H/D exchange chemoselectively at α-CH_2 of amines, where α-CH_2 related to alcohol functionality[16a] remains unaffected (entry 6), offering further opportunity for selective deuteration toward amines α-CH_2 by catalyst **1**. Embedded with sulfur heteroatom, methionine displayed efficient H/D exchange at the α-CH_2 of amine (entry 7, Table 3). Further, moderate to excellent deuteration occurred on isoleucine, aspartic acid, methyl ester of serine, valine, and cyclic amino acid proline (entries 8−12).

Notably, the β-deuteration is observed only on linear acyclic primary amines such as pentyl-, hexyl-, heptyl-, and phenethyl-amines (2−9%). On other primary amines, primary diamines, secondary amines, and amino acids no such β-deuteration is

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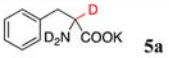
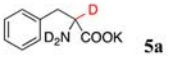
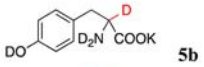
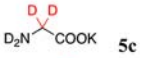
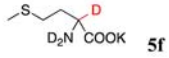
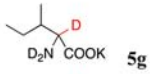
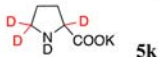
Table 3. Selective α-Deuteration of Amino Acids[a]

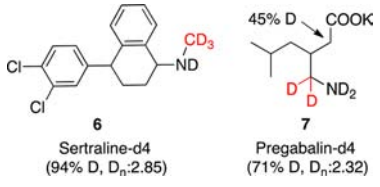
entry	product		deuteration (%)[b,d]	D_n[c]
1		5a	84	0.84
2[e]		5a	17	0.17
3[f]		5b	40	0.4
4[f,g]		5c	89	1.78
5		5d	71	0.71
6[f]		5e	86	0.86
7		5f	70	0.7
8		5g	50	0.5
9		5h	73	0.73
10[f]		5i	93	0.93
11		5j	80	0.8
12[f,h]		5k	80, 50	1.8

[a]Amino acid (0.5 mmol), KOH (0.5 mmol), and D_2O (0.6 mL, 30 mmol) were charged in a scintillation vial and stirred for 30 min at rt. Then catalyst **1** (0.005 mmol, 1 mol %) in 1,4-dioxane (stock solution) was added and the mixture heated to 135 °C for 36 h. [b]See Table 1. [c]See Table 1. [d]Calculated for the products in the reaction mixture. [e]Control experiment, verified twice. [f]Maximum theoretical % deuterium incorporation is 96.77%. [g]1,4-Dioxane (40 μL) was used as internal standard. [h]Catalyst used (0.01 mmol).

observed, indicating the high selectivity of this method for the α-deuteration of amine functionalities.

Sertraline **6** is an antidepressant, used for the treatment of anxiety disorders, post-traumatic stress disorder (PTSD), and premenstrual dysphoric disorder (PMDD). When reacted with deuterium oxide and catalyst **1** under the experimental conditions established for the amino acids, 94% deuteration (96.77% maximum theoretical % deuterium) at the *N*-methyl protons of sertraline occurred (Scheme 1). Deuteration occurred selectively on *N*-methyl protons over the α-proton on the cyclohexyl ring, perhaps due to the steric hindrance. Similarly, pregabalin **7**, a medicine used for treating pain caused by nerve

Scheme 1. Catalytic Deuteration of Pharmaceuticals



damage due to diabetes, shingles (herpes zoster) infection, and fibromyalgia, exhibited 71% deuteration at the α-CH_2 protons to the amine group. Conditions for deuteration catalyzed by **1** can be further optimized for individual drug molecules to achieve higher deuteration.

Stoichiometric reactions of complex **1** with benzylamine at rt led to immediate formation of a new cationic mononuclear Ru(IV) hydride complex **2**, resulting from an unprecedented N–H bond activation[20] of benzylamine, which showed the corresponding hydride signal at δ −5.5 ppm in ^{1}H NMR spectroscopy.[21] The structure of complex **2** is unequivocally corroborated using single-crystal X-ray analysis,[22] which displayed capped pseudo octahedral geometry around the ruthenium center (Figure 1). Upon using isolated **2** (0.5 mol

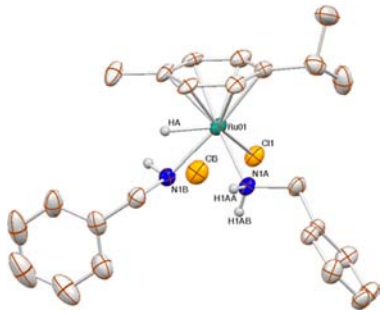
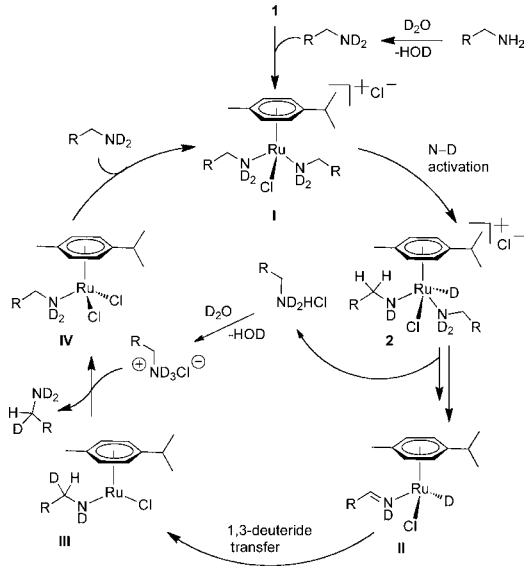


Figure 1. X-ray structure of [{(η^6-*p*-cymene)RuHCl}($NHCH_2Ph$)(NH_2CH_2Ph)Cl (**2**). ORTEP diagram is drawn with 50% probability.

%) as a catalyst, similar deuteration as for catalyst **1** was obtained for benzylamine, indicating the involvement of **2** in catalysis. Further, addition of mercury (50 mol %) to the catalytic deuteration (**1**, 0.5 mol %) of benzylamine and hexylamine resulted in an insignificant effect and 90% and 83% α-deuteration occurred, respectively, indicating (although not proving) the involvement of molecular organometallic intermediates.

On the basis of these experimental observations, a catalytic cycle is proposed as described in Scheme 2. The reaction of **1** with amine provided an initial cationic ruthenium(II) coordina-

Scheme 2. Proposed Mechanism for α-Selective Deuteration of Amines and Amino Acids



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tion complex **I**. Subsequent N−H bond activation of a coordinated amine provided the observed mononuclear Ru(IV) cationic complex **2**. Further β-hydride elimination and concomitant dissociation of ammonium salt generates imine ligated Ru(II) complex **II**. A 1,3-deuteride transfer on **II** leads to the reduction of ligated imine to provide amide coordinated Ru(II) intermeidate **III**. Further, reaction of **III** with quaternary amine and subsequent decoordination of amine from **III** provided partial (α-CHD) deuterated amine and a Ru(II) complex **IV**, which upon coordination of a benzylamine regenerates **I** and closes a catalytic cycle.

In conclusion, a ruthenium-catalyzed selective α-deuteration of primary amines, secondary amines, amino acids and commercial drugs is demonstrated. Stoichiometric reactions revealed the involvement of Ru(IV) intermediate. The mechanism involving an unprecedented N−H activation by a cationic ruthenium complex and subsequent 1,3-deuteride transfer to in situ formed imine is proposed. High deuterium incorporation, exceptional selectivity for α-CH_2 protons to the amine functional group, and low loadings of catalyst **1** make this protocol attractive and advantageous for both laboratory and large-scale preparation of highly useful deuterated amines and amino acids. Applications of **1** in other deuteration reactions and catalysis based on N−H activation are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02978.

Experimental procedures and spectral data. Single-crystal X-ray data of complex **2** (CCDC 1481309) (PDF)

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Notes

The authors declare no competing financial interest.

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(21) Reaction of **1** with benzylamine in H_2O also led to immediate formation of **2** at rt. Upon heating, **2** remained with decreased intensity and two new signals appeared in hydride region of ^{1}H NMR (δ −19.02 and −19.20 ppm), and the corresponding complexes remain elusive to isolation and characterization.

(22) Two molecules were present in unit cell. See Figure S1.

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