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Ruthenium-catalyzed selective α-deuteration of aliphatic nitriles using D_2O†

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Selective catalytic α-deuteration of aliphatic nitriles using deuterium oxide as a deuterium source is reported. A PNP–ruthenium pincer complex catalyzed the α-deuteration of aliphatic nitriles including acetonitrile. Efficient deuteration occurred with a low catalyst load (0.2 to 0.5 mol%) and under mild conditions. A [2+2] cycloadduct formation from nitrile functionality and a deprotonated catalytic intermediate, followed by an imine–enamine tautomerization and a H/D exchange between the enamine intermediate and deuterium oxide leading to the selective deuteration at the α-position of the nitrile, is proposed as a plausible reaction mechanism.

Deuterium isotopes introduced into organic compounds exert their influence in enhancing the molecular properties of the resultant labelled products. Such labelled molecules have found widespread application[1] as NMR solvents, polymeric materials,[2] chemical and biological probes and are commonly used as internal standards in quantitative mass spectral studies[3] and drug development.[4] The notable importance of such deuteration is that the introduction of deuterium labels on the metabolically susceptible C–H bonds of a compound can increase its metabolic stability and thus enhance its therapeutic efficacy. SD-809 (the deuterium-labelled version of the commercial drug tetrabenazine) was tested on human beings with Huntington's disease and has already been approved by the US FDA (as Austedo®) after successful phase III clinical trials.[5,6] There are more such deuterium-containing drug candidates under evolution.

Nitriles are an important class of organic compound, as many of them are bioactive molecules and there are more than 30 nitrile-containing compounds currently being used as pharmaceuticals.[7] In addition, there are several nitrile-embedded candidates under clinical development.[8] Acetonitrile-d_3 is a commonly used NMR solvent and other deuterated nitrile compounds are used as chemical probes. Despite the widespread use of deuterated nitrile compounds, synthetic methods for the preparation of aliphatic nitriles are scarce and they suffer from a low level of deuterium incorporation, the requirement of polar substituents on the γ-position, limited substrate scope and the repetition of tedious processes to achieve higher deuteration.[9,10] Thus, the selective catalytic deuteration of nitriles using deuterium oxide is desirable and atom economical.

We have reported the selective α-deuteration of primary alcohols and the α,β-deuteration of secondary alcohols using ruthenium pincer complex [(PNP^{Ph})RuHCl(CO)] **1** (PNP = bis(2-(diphenylphosphino)ethyl)amine) and deuterium oxide, in which we have demonstrated the facile O–H/O–D bond activation of alcohols and deuterium oxide by **1** in the presence of a base.[11] Complex **1** also catalyzed the selective deuteration of the sp-C–H bond of terminal alkynes.[12] Recently, we have also reported the selective α-deuteration of primary and secondary amines, as well as amino acids using deuterium oxide.[13] A mono-hydrido-bridged dinuclear ruthenium complex[14] catalyzed this chemo- and regioselective transformation and the reaction proceeded *via* N–H activation.[13] In a continuation of our efforts to develop efficient and direct deuteration of organic compounds using deuterium oxide, herein we report the selective α-deuteration of aliphatic nitriles using catalyst **1**.

Preliminary studies began on the deuteration of acetonitrile. Upon the reaction of acetonitrile (0.5 mmol) with catalyst **1** (0.1 mol%) and KO^{t}Bu (0.5 mol%) in deuterium oxide at 60 °C for 24 h, 49% deuteration was observed. A similar reaction at 70 °C provided 92.3% deuteration. When 0.2 mol% of catalyst **1** was used, an efficient deuteration of 95.7% (against a theoretical maximum of 96.4%) was obtained (entry 1 in Table 1). Other aliphatic nitrile compounds were subjected to the catalytic deuteration under the optimized experimental conditions. Aliphatic linear nitriles underwent selective deuteration only at the α-CH_2 protons of the nitrile functionality and no detectable deuteration was observed at the β- and other CH protons. However, the % of deuteration showed the substrate dependence.

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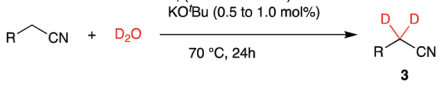
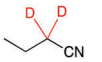
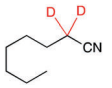
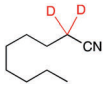
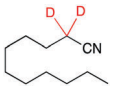
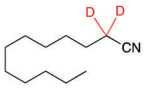
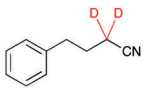
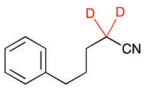
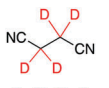
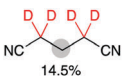
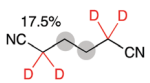
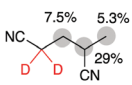
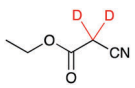
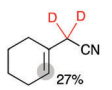
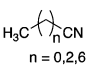
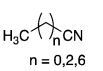
† Electronic supplementary information (ESI) available: Experimental procedures, NMR spectra of deuterated aliphatic nitriles and their spectral data. See DOI: 10.1039/c8cc03971b

Table 1 Selective α-deuteration of aliphatic nitriles[a]



Entry	Product		O.D.[b] (%)	T.D.[c] (%)	Dn[d]
1[e]	CD_3CN	**3a**	95.7	96.4	2.87
2		**3b**	63	97.6	1.26
3		**3c**	81	97.6	1.62
4		**3d**	81	97.6	1.62
5		**3e**	64	97.6	1.28
6		**3f**	62	97.6	1.24
7		**3g**	72	97.6	1.44
8		**3h**	50	97.6	1.00
9[e]		**3i**	93.3	95.2	3.73
10[e]		**3j**	91.5	93	3.95
11[e]		**3k**	88.5	90.9	4.24
12[e]		**3l**	94	97.6	2.47
13[e]		**3m**	94	97.5	1.88
14		**3n**	94.5	96.4	2.16
15[f]			NR		
16[g]			NR		

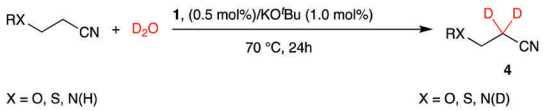
[a] Aliphatic nitrile (0.5 mmol), catalyst **1** (0.001 mmol, 0.2 mol%), KO^{t}Bu (0.002 mmol, 0.5 mol%) and D_2O (0.4 mL, 20 mmol) were charged in a scintillation vial and heated to 70 °C. Entries 2–8: catalyst load used 0.0025 mmol, 0.5 mol%; base 1 mol%. [b] Observed % of deuteration (O.D.) calculated from the integration of the residual signals in the ^{1}H NMR spectra. [c] Maximum theoretical % of deuteration (T.D.). [d] Average number of catalytically introduced deuterium atoms per molecule. [e] Dichloroethane (0.5 mmol, 39.5 μL) was used as the internal standard. [f] 1 mol% of KO^{t}Bu, no catalyst. [g] Without catalyst and base. NR – No reaction.

The reaction of butyronitrile with catalyst **1** (0.2 mol%) provided only 23% deuteration. The use of 0.5 mol% of catalyst **1** resulted in 63% deuteration (entry 2 in Table 1). Under similar conditions, octanenitrile, nonanenitrile, undecanenitrile and dodecanitrile showed 62–81% α-deuteration. 4-Phenylbutanenitrile and 5-phenylpentanenitrile displayed 72% and 50% deuterium incorporation, respectively, at the α-CH_2 positions (entries 7 and 8 in Table 1). The ruthenium-catalyzed conversion of nitriles to amides is known for both aromatic and aliphatic nitriles in the presence of water.[15] However, this developed protocol selectively deuterates the α-position of the nitriles and the CN group remains intact.

Aliphatic dinitriles were found to be more reactive than linear aliphatic nitriles and facile selective deuteration occurred at both α-positions with 0.2 mol% of catalyst **1**. Succinonitrile exhibited excellent deuteration at both α-CH_2 positions with a high D content (Dn: 3.73, entry 9 in Table 1). Similarly, glutaronitrile, adiponitrile and 2-methylglutaronitrile showed facile predominant deuteration at both α-CH_2 positions (entries 10–12 in Table 1). However, these dinitriles also showed deuteration at the β-position in the range 5.3–17.5%, which eventually resulted in a higher deuterium incorporation (2.47 to 4.24 Dn), making these molecules suitable for use as an internal MS standard in the analysis of life science samples.[16] Furthermore, ethyl cyanoacetate displayed efficient deuteration (94%) at the α-position (entry 13 in Table 1). 1-Cyclohexeneacetonitrile displayed a deuteration of 94.5% against a theoretical deuteration of 96.4% (entry 14 in Table 1). Control experiments performed under the standard experimental conditions with or without base and in the absence of the catalyst resulted in no detectable deuteration of acetonitrile, which confirms that the deuteration is truly a catalytic process (entries 15 and 16 in Table 1).

Next, the deuteration of heteroatom- and heterocycle-tethered aliphatic nitriles was explored. Initially 0.2 mol% of complex **1** was used for the reaction, which resulted in partial deuteration. Upon using 0.5 mol% of **1** and 1 mol% of base, selective α-deuteration occurred on oxygen-attached 3-(hexyloxy)propanenitrile, 4-(hexyloxy)hexanenitrile, 3-((2,3-dihydro-1*H*-inden-2-yl)oxy)propanenitrile and 3,3′-(pentane-1,5-diylbis(oxy))-bis(propanenitrile) (entries 1–4 in Table 2). A minor amount of β-CH_2 deuteration was also observed (entries 1 & 4). Notably, sulfur-containing 3-(benzylthio)propanenitrile displayed exclusive deuteration on the α-position (entry 5 in Table 2). Likewise, nitrogen-attached linear aliphatic nitriles showed a moderate to high α-deuteration of 67 to 85% (entries 6–9 in Table 2). Similarly, other amines with nitrile functionality such as 3-(dipropylamino)propanenitrile and 3-(piperidin-1-yl)propanenitrile resulted in a higher degree of α-deuteration (entries 10 and 11 in Table 2). Heterocyclic compounds are well tolerated and deuteration occurred only at the α-CH_2 to the nitrile group. Indole-containing aliphatic nitriles were examined, and they showed (entries 12 and 13 in Table 2) 67 to 94% deuteration (the maximum theoretical % of deuteration is 97.5%). Unlike in the Ru- or Ir-catalyzed deuteration of indole derivatives, the highly active C2 and C3 positions are not affected by the C–H/D exchange.[17] The α-methylene protons of 3-phenathiazine propionitrile were exclusively deuterated by catalyst **1** and the

Table 2 Selective α-deuteration of heteroatom-containing aliphatic nitriles[a]



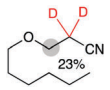
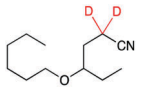
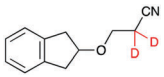
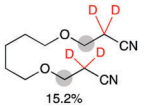
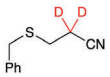
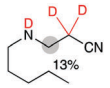
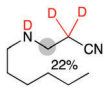
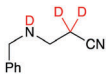
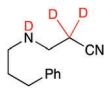
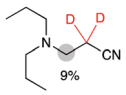
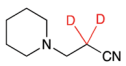
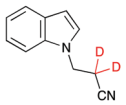
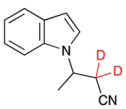
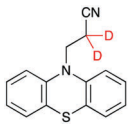
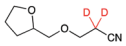
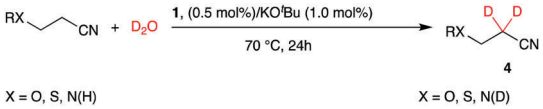
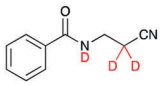
Entry	Product		O.D.[b] (%)	T.D.[c] (%)
1		**4a**	95	2.36
2		**4b**	89	1.78
3		**4c**	95	1.90
4[d]		**4d**	80	3.80
5		**4e**	91.5	1.83
6		**4f**	85	1.96
7		**4g**	67	1.78
8		**4h**	69	1.38
9		**4i**	68.5	1.37
10		**4j**	89	1.96
11		**4k**	94	1.88
12		**4l**	94	1.88
13		**4m**	67	1.34
14		**4n**	79	1.58
15		**4o**	96.5	1.93

Table 2 (*continued*)



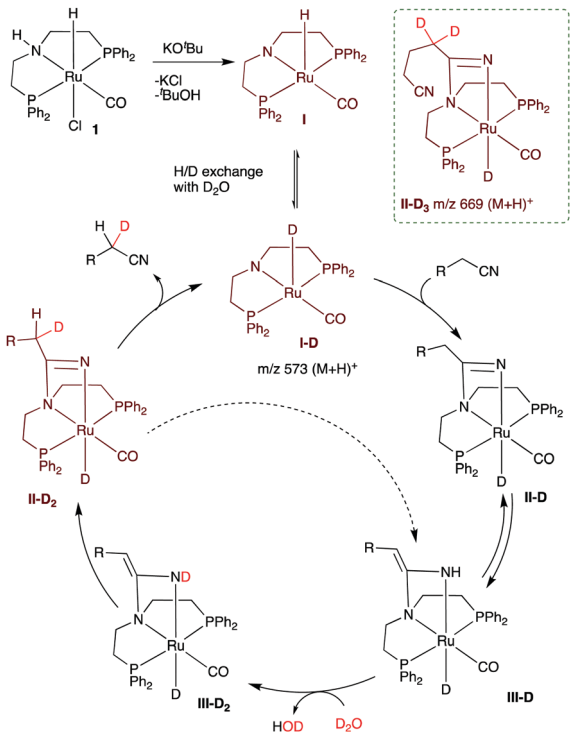
Entry	Product		O.D.[b] (%)	T.D.[c] (%)
16		**4p**	94	1.88

[a] Nitrile (0.5 mmol), catalyst **1** (0.0025 mmol, 0.5 mol%), base (1 mol%), and D_2O (0.4 mL, 20 mmol) were charged in a scintillation vial and heated to 70 °C. [b] Calculated from the integration of the residual signals in the ^1H NMR spectra. The maximum theoretical % of deuteration was 97.5%. [c] Average number of catalytically introduced deuterium atoms per molecule. [d] The maximum theoretical % of deuteration was 90.9%.

aromatic protons were unaffected. When 3-((tetrahydrofuran-2-yl)methoxy)propanenitrile was subjected to catalysis, 96.5% deuteration was attained at the α-CH_2 positions. Amide-containing nitriles provided 94% deuteration at the α-position (entry 16 in Table 2).

Furthermore, the ^2H NMR spectra that were recorded for the representative compounds clearly confirmed the α-selective deuteration of aliphatic nitriles (see the ESI†).

To understand the reaction mechanism, the deuteration reactions catalyzed by complex **1** were probed using the ESI-MS analyses of the reaction mixtures. Upon reaction of **1** with a base, an unsaturated amide-ligated intermediate **I** was



Scheme 1 Proposed mechanism for the selective deuteration of aliphatic nitriles.

formed,[12] which underwent Ru–H/D exchange with deuterium oxide. This afforded intermediate complex **I-D**, which was observed *in situ* using ESI-MS analysis (*m*/*z* 573 $(M + H)^+$). Nitrile coordination to the intermediate **I-D** led to the formation of a [2+2]-cycloadduct **II-D**, which was in equilibrium with its enamine form **III-D**. H/D exchange between the enamine of **III-D** and deuterium oxide generated **III-D2**. Further tautomerization, perhaps assisted by the base and deuterium oxide, led to intermediate **II-D2**.[18,19] Nitrile dissociation from **II-D2** could provide mono-deuterated nitrile or tautomerization could result in the formation of a **III-D**-type intermediate, which would undergo further H/D exchange and tautomerization to provide a **II-D3** intermediate that could liberate nitrile with complete deuteration at the α-position and regenerate the intermediate **I-D** to close the catalytic cycle. Interestingly, a **II-D3**-type intermediate (*m*/*z* 669 $(M + H)^+$) was observed in the ESI-MS analysis of the deuteration reaction of glutaronitrile catalyzed by **1** (Scheme 1).

In conclusion, we have demonstrated highly efficient and selective α-deuteration of aliphatic nitriles catalyzed by a ruthenium pincer complex **1**. The ability of the unsaturated intermediate (**I-D**) formed from **1** to provide a [2+2] cycloadduct with nitriles and subsequent tautomerization to an enamine form plays an important role in the catalytic deuteration reactions. This unprecedented catalytic protocol operates under mild conditions with low catalyst loading. Notably, this method can be applied for the large-scale synthesis of acetonitrile-d_3 and other useful deuterated nitrile compounds.

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Conflicts of interest

There are no conflicts to declare.

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