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Selective α-Deuteration of Cinnamonitriles using D_2O as Deuterium Source

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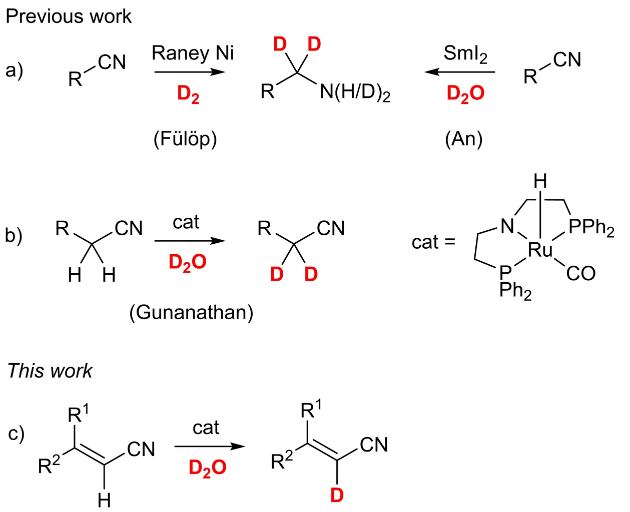
Abstract: The selective α-deuteration of α,β-unsaturated nitriles using the strong base ^{t}BuOK or a metal-ligand cooperative Ru pincer catalyst is described. With D_2O as deuterium source and glyme as solvent at 70 °C, ^{t}BuOK is an efficient catalyst for deuteration at the α-C(sp^2) position of cinnamonitriles, providing access to a broad range of deuterated derivatives in good to excellent yields and with very high levels of deuterium incorporation. While the ^{t}BuOK-catalysed protocol does not tolerate base-sensitive functional groups, cinnamonitrile derivatives containing a benzylic bromide or ester moiety were deuterated in excellent yields using Milstein's ruthenium PNN pincer catalyst. Moreover, the activity for H/D exchange of the metal-ligand cooperative Ru catalyst is found to be significantly higher than that of ^{t}BuOK, allowing reactions to proceed well even at room temperature. A mechanistic proposal is put forward that involves deprotonation of the cinnamonitrile α-CH position when using ^{t}BuOK as catalyst, whereas H/D exchange catalysis with the Ru PNN pincer likely proceeds via (reversible) oxa-Michael addition of D_2O.

Keywords: homogeneous catalysis; deuterium; metal-ligand cooperation; unsaturated nitriles

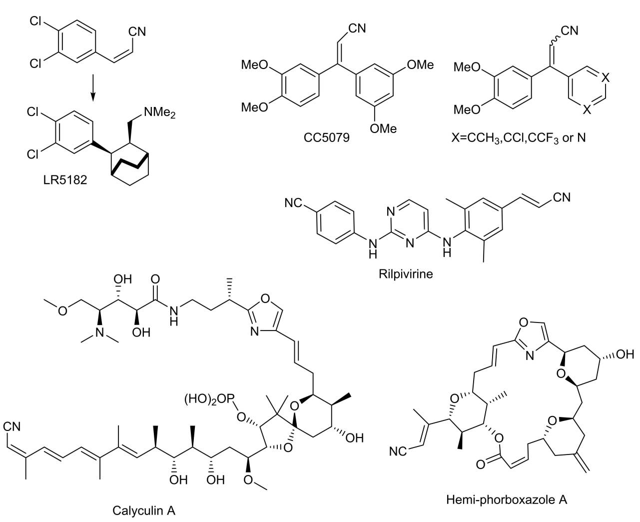
Introduction

Isotopically labelled compounds in which one or more hydrogen (^1H) atoms are substituted for the heavier isotopes deuterium (^2H or D) or tritium (^3H or T) are of interest in a wide variety of contexts. For example, isotopic labelling is important for studies related to reaction mechanisms (e.g., kinetic isotope effects, delineating site selectivity).[1] Moreover, deuterium- or tritium-labelled compounds have been used extensively in the medicinal chemistry field to study absorption, distribution, metabolism, and excretion (ADME) of drug candidates.[2] Drugs that are deuterated in selected positions can have substantially altered pharmacokinetics and metabolic stability,[3] and thus offer the potential to slow down clearance from the body by a decrease in the rate of oxidation of the C–D relative to C–H bonds. The 2017 approval of Deutetrabenazine, which contains two OCD_3 groups, by the U.S. Food and Drug Administration (FDA) as the first deuterium-containing drug presents an important milestone,[4] and many more deuterated drug candidates are in clinical trials.[5]

Synthetic methods to achieve deuterium incorporation in organic molecules often rely on H/D exchange between the (relatively inert) C–H bonds and either D_2O or D_2 as the deuterium source. While a large variety of catalysts have been developed for H/D exchange of both aliphatic and aromatic C–H bonds,[6] novel methods for the straightforward, selective introduction of deuterium are in high demand. Organic nitriles are an attractive starting point for the synthesis of deuterated N-containing compounds: reduction affords imines and amines that are deuterated at the position α to the nitrogen atom (Scheme 1a),[7] whereas the C–H bond next to the nitrile moiety is sufficiently acidic to exchange with D_2O under mild conditions (Scheme 1b).[8] The latter reaction was reported as early as 1957 using base catalysis,[8a] and more recently Gunanathan reported efficient Ru catalysts based on an aliphatic PNP pincer scaffold for the α-deuteration of



Scheme 1. H/D exchange in organic nitriles to deuterated N-containing building blocks.



Scheme 2. Biologically active compounds containing the unsaturated nitrile motif including anti-cancer agents (for example, CC-5079[13] and derivatives;[14] Phorboxazoles[15]) and anti-HIV agents (Rilpivirine[16]).

saturated aliphatic nitriles.[8b] The unsaturated nitrile motif is present in a variety of biologically active compounds (Scheme 2), and further transformation of the CN group provides access to amides and carboxylic acids. Despite major advances in the synthesis of stereodefined alkenyl nitriles that have recently been reported,[9] the catalytic deuteration of the sp^2-carbons of unsaturated nitriles has remained underdeveloped.

In 1963, Hauser and co-workers reported that *trans*-cinnamonitrile could be deuterated at the α-position using a ten-fold excess of EtOD in the presence of 10 mol% NaOEt, but the yield was moderate (60%) and the product was obtained as a *cis*/*trans* mixture with a limited extent of deuterium-labelling (75%).[10]

The group of Feit developed the chemistry of mono- and dilithiated cinnamonitriles, and demonstrated α-monodeuteration as well as α,β-dideuteration using LDA/MeOD,[11] but synthetic applications of this methodology are limited due to the use of (super) stoichiometric amounts of strong base and limited deuterium incorporation. To date, the Wittig-Horner reaction is the only method to obtain α-deuterated cinnamonitrile with >95% deuterium incorporation.[12]

Selective catalytic α-deuteration of styrenes was recently reported by Bandar and co-workers, by realizing that base-catalysed nucleophilic addition of alcohols to styrenes was kinetically fast but endergonic for some alcohol/solvent combinations.[17]

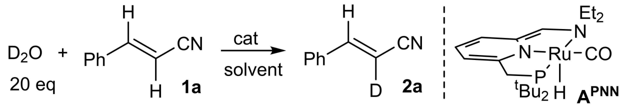
We hypothesised that our protocol for oxa-Michael additions to α,β-unsaturated nitriles using a metal-ligand cooperative Ru pincer catalyst[18] could similarly lead to selective α-deuteration under conditions where conjugate addition is fast yet thermodynamically unfavourable. The use of D_2O as source of deuterium is desirable because it is cheap and readily available, but given that the Milstein-type Ru catalysts also show high activity for nitrile hydration,[19] we needed to minimize this potential side-reaction. Here we describe the results of our studies into the deuteration of α,β-unsaturated nitriles, and describe two different catalytic protocols for the selective α-deuteration of these compounds.

Results and Discussion

We started our investigation with the benchmark substrate cinnamonitrile **1a**, using 1.5 mol% of the metal-ligand cooperative Ru PNN pincer catalyst $\mathbf{A}^{\mathbf{PNN}}$ (structure shown in Table 1). Conducting the reaction at 0.25 mmol scale in d_8-THF solvent (0.5 mL) with 5 mmol D_2O, we were able to achieve 37% deuteration (to **2a**) after a day at room temperature (entry 1 in Table 1). Stirring the reaction for another 24 hours afforded 67% deuterium incorporation.

From the ^{1}H NMR spectra in d_8-THF, it is clear that the intensity of the doublet of the α-proton at 6.22 ppm decreased over time and the doublet of the β-proton at

Table 1. Optimization of H/D exchange at the α-position of cinnamonitrile **1 a** with D_2O.[a]



entry	solvent	cat (mol%)	temp (°C)	deuteration (%)[b]
1	d_8-THF	$\mathbf{A}^{PNN}$ (1.5)	rt	37
2	d_8-THF	$\mathbf{A}^{PNP}$ (1.5)	rt	**1a/2a** + amide
3	toluene	$\mathbf{A}^{PNN}$ (1.5)	rt	39
4[c]	MTBE	$\mathbf{A}^{PNN}$ (1.5)	rt	36
5[d]	DCE	$\mathbf{A}^{PNN}$ (1.5)	rt	4
6	1,4-dioxane	$\mathbf{A}^{PNN}$ (1.5)	rt	-
7	glyme	$\mathbf{A}^{PNN}$ (1.5)	rt	95
8	glyme	^{t}BuOK (2)	rt	32
9[e]	glyme	^{t}BuOK (2)	70	92

[a] Reaction conditions: cinnamonitrile (0.25 mmol), D_2O (5 mmol) and catalyst in 0.5 mL of solvent, N_2 atmosphere, 1 day.
[b] Degree of deuteration was determined by ^{1}H NMR spectroscopy.
[c] MTBE, methyl tert-butyl ether.
[d] DCE, 1,2-dichloroethane.
[e] Reaction time of 5 hours.

7.48 ppm slowly converted to a singlet without change in integration (Figure 1). At the same time, the peak of HDO also increased. These observations indicate that *trans*-cinnamonitrile was selectively deuterated at the α-position in the presence of a catalytic amount of $\mathbf{A}^{PNN}$. No H/D exchange was observed in the absence of $\mathbf{A}^{PNN}$. The related PNP-pincer catalyst $\mathbf{A}^{PNP}$ instead resulted in a mixture of (deuterated) nitrile and the corresponding amide product (also partially deuterated) (entry 2 in Table 1), which indicates that under these conditions $\mathbf{A}^{PNP}$ is active for both H/D exchange and nitrile hydration.[19] The deuterated amide is obtained due to hydration of d_1-cinnamonitrile (**2 a**), rather than H/D exchange of the amide: control experiments with cinnamide/D_2O did not result in deuteration at the CH bonds.

A screening of different solvents with $\mathbf{A}^{PNN}$ as catalyst gave very similar results for relatively non-polar solvents such as toluene and MBTE, whereas poor conversion was obtained in DCE (1,2-dichloroethane) or dioxane (entries 3–6 in Table 1). Surprisingly, the use of glyme (dimethoxyethane) as a solvent

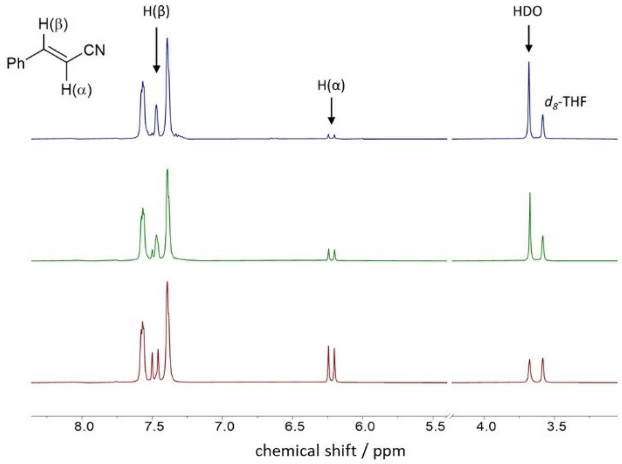


Figure 1. ^{1}H NMR spectra of $\mathbf{A}^{PNN}$-catalysed H/D exchange of *trans*-cinnamonitrile (**1 a**) with D_2O in d_8-THF at room temperature. Spectra are taken after 9 h (bottom), 24 h (middle) and 48 h (top).

resulted in 95% deuteration under these conditions (rt, 24 h; entry 7 in Table 1), which indicates H/D exchange to approach the expected statistical distribution based on the amount of deuterium present (20 equiv. of D_2O relative to cinnamonitrile). Subsequent experiments thus used glyme as the solvent of choice.

Monitoring the deuteration in glyme by ^{1}H NMR spectroscopy was facilitated by solvent suppression methods, which allowed direct observation of the signals of cinnamonitrile in non-deuterated organic solvent (area of interest: >6.0 ppm, see ESI Figure S1).

To confirm the role of the Ru-complex $\mathbf{A}^{PNN}$ in the reaction, a series of control experiments were conducted under the same reaction conditions. The Lewis acid $Sc(OTf)_3$ did not result in H/D exchange in cinnamonitrile, and while the Brønsted bases KOH and ^{t}BuOK gave some deuterated product, the extent of H/D exchange is significantly less (17 and 32%, respectively), demonstrating the beneficial role of the Ru catalyst (see ESI Table S1 and entry 8 in Table 1). Two other representative Ru complexes, Milstein's acridine-based pincer catalyst and the dichloro(p-cymene)ruthenium(II) dimer (see ESI Table S1), were also tested but were either less effective (28% D incorporation) or showed no reaction at all, respectively.

Recognizing that the strong base ^{t}BuOK is a cheap and attractive alternative to the Ru PNN pincer catalyst when the unsaturated nitrile does not possess base-sensitive functional groups, we found that an increase in the reaction temperature to 70 °C allows a high α-deuteration level of cinnamonitrile **1 a** (92%) also when using ^{t}BuOK as catalyst, even after only 5 hours (entry 9 in Table 1). For comparison, the reaction profiles for H/D exchange using both A^{PNN} and ^{t}BuOK are shown in Figure 2, highlighting that the Ru-catalyst A^{PNN} shows superior performance in H/D exchange compared to ^{t}BuOK when carried out at room temperature, but ^{t}BuOK becomes competitive at elevated temperature.

It is worth to mention that both A^{PNN}- and ^{t}BuOK-catalysed reactions yield the α-deuterated product **2a** exclusively: ^{1}H NMR integration as well as the lack of C–D coupling in the ^{13}C(^{1}H) NMR spectra indicate that the β-CH bond does not engage in H/D exchange.

Overall, these initial observations allowed us to develop two protocols for selective α-deuteration of unsaturated nitriles. First, we will focus on the tBuOK-catalysed reaction, and subsequently describe H/D-exchange reactions with substrates that possess base-sensitive functional groups by using APNN as catalyst.

Catalytic H/D exchange using ^{t}BuOK. The substrate scope of ^{t}BuOK-catalysed H/D-exchange was investigated. The reactions were conducted at 70 °C in glyme solvent, with 20 equiv. of D_2O as deuterium source and using 2 mol% of catalyst. As shown in Table 2, cinnamonitrile derivatives with electron-donating substituents (**1b**, *p*-Me; **1c**, *p*-OMe; **1d**, *p,m*-(OMe)$_2$) were less efficiently deuterated than the parent cinnamonitrile **1a**, and were obtained with only moderate deuterium incorporation (24–68%, entries 3, 5, 7). Qualitatively, these reactions were initially fast, but then the rates decreased until no further conversion occurred anymore after ca. 6 hours. It appears that these substrates lead to side products that deactivate the catalyst, which we have not investigated further. Increasing the catalyst loading to 10 mol% of ^{t}BuOK resulted in high deuteration levels of ca. 90% and excellent isolated yields (>90%) for the products **2b–d** within 5 hours of reaction time (entries 4, 6, 8). Unfortunately, the electron-rich *p*-Me_2N substituted derivative **1e** did not work even using 10 mol% of catalyst (entry 9). When examining the effect of electron-withdrawing groups, we found that also the *p*-F derivative **1f** showed no H/D exchange under the standard conditions (2 mol% ^{t}BuOK), but in this case an increase in catalyst loading to 10 mol% restored activity and afforded a high degree of deuteration (92%; entry 10). The *ortho*-, *meta*- and *para*-chloro

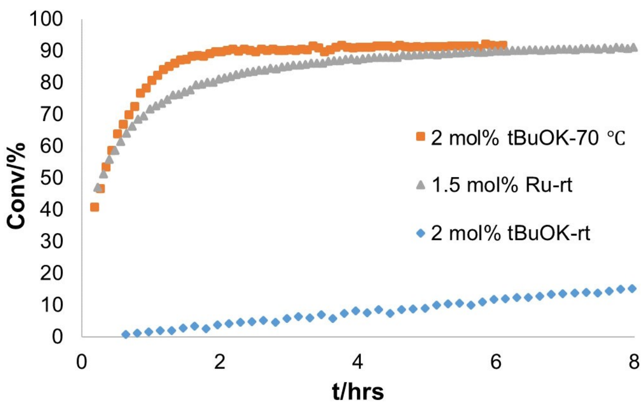
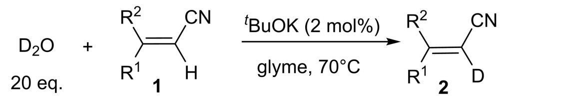


Figure 2. Conversion vs. time plot for H/D exchange of cinnamonitrile (**1a**) with D_2O in glyme [Ru = A^{PNN}].

Table 2. Substrate scope of ^{t}BuOK-catalysed selective α-deuteration of nitriles with D_2O.[a]



entry	compound	R^1	R^2	time (h)	D%	yield (%)[e]
1[b]	**1a**	Ph	H	5	95(>99)	94
2[c]	**1a**	Ph	H	5	98	97
3	**1b**	*p*-Me-Ph	H	6	24	nd
4[d]	**1b**	*p*-Me-Ph	H	5	94	89
5	**1c**	*p*-OMe-Ph	H	6	68	nd
6[d]	**1c**	*p*-OMe-Ph	H	4.7	91	96
7	**1d**	*p,m*-(OMe)$_2$-Ph	H	6	68	nd
8[d]	**1d**	*p,m*-(OMe)$_2$-Ph	H	2.8	92	86
9[d]	**1e**	*p*-NMe$_2$-Ph	H	-	-	-
10[d]	**1f**	*p*-F-Ph	H	2.8	92	89
11	**1g**	*o*-Cl-Ph	H	0.75	97	92
12	**1h**	*m*-Cl-Ph	H	0.75	96	91
13	**1i**	*p*-Cl-Ph	H	0.75	96	93
14	**1j**	*p*-Br-Ph	H	0.75	95	90
15	**1k**	2-Py	H	1	97	86
16	**1l**	2-furyl	H	3	95	83
17	**1m**	2-thienyl	H	1	96	90
18	**1n**	Ph	Ph	4.25	91	97
19	**1o**	*p*-F-Ph	Cl	-	-	-

[a] Reactions were carried out with 0.25 mmol nitrile in 0.5 ml solvent, and deuteration determined by ^{1}H NMR with solvent suppression.
[b] >99% deuterium labelling was obtained by a second run with addition of fresh solvent, D_2O and cat.
[c] Reaction was carried out at the gram scale.
[d] Reactions were carried out with 10 mol% catalyst.
[e] Isolated yield.

substituted substrates **1g–i** as well as the *para*-bromo derivative **1j** (entries 11–14) were efficiently deuterated with 2 mol% of ^{t}BuOK in only 45 min. Unsaturated nitriles with heteroaromatic β-substituents were subsequently tested. Substrates with 2-pyridyl (**1k**), 2-furyl (**1l**) or 2-thienyl groups (**1m**) were all tolerated and afforded the α-deuterated products in high isolated yield and with excellent levels of deuteration (entries 15–17). The β-disubstituted substrate 3,3-diphenylacrylonitrile (**1n**) was deuterated with equally high efficiency under standard conditions (entry 18). However, no H/D exchange occurred in the case of (Z)-3-chloro-3-(4-fluorophenyl) acrylonitrile (**1o**) (entry 19), which instead resulted in base-induced elimination of HCl to form the alkyne product 3-(4-fluorophenyl) propiolonitrile.

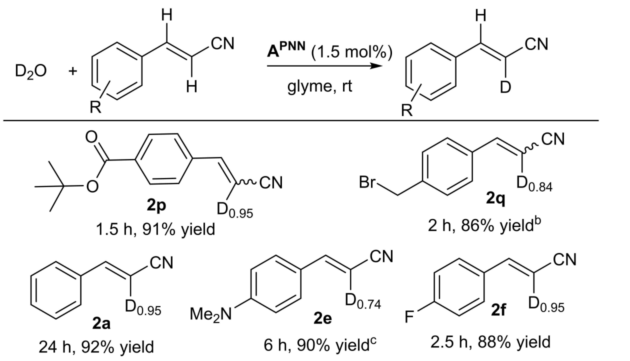
Catalytic H/D exchange using A^{PNN}. The unsaturated nitriles described above all undergo α-deuteration in an operationally simple manner, but substrates containing base-sensitive functional groups are likely incompatible with the use of strongly Brønsted basic alkali metal alkoxides or hydroxides. Indeed, attempts to achieve H/D exchange of the cinnamonitrile derivative **1p** having a base-sensitive *t*-butyl ester group gave no H/D exchange using ^{t}BuOK, likely because the benzoic acid that is generated upon ester hydrolysis quenches the base catalyst.

Similarly, substrate **1q** containing a benzylic bromide is not deuterated using the ^{t}BuOK/D_2O protocol, which can be ascribed to competing S_N2 substitution to give the corresponding benzyl alcohol. In contrast to ^{t}BuOK, catalyst A^{PNN} performs well at room temperature and leads to high deuteration levels in these substrates, and the α-deuterated products could be isolated in > 85% isolated yield (Table 3). Remarkably, both the base-sensitive ester (**2p**) and benzylic bromide (**2q**) are retained in the final product using the ruthenium catalyst A^{PNN} under these mild conditions. Moreover, the highly electron-rich NMe_2-substituted substrate **1e** did not show any H/D exchange using ^{t}BuOK as catalyst, but was smoothly converted to the α-deuterated derivative using the Ru catalyst A^{PNN}, albeit that a higher reaction temperature of 70 °C was required.

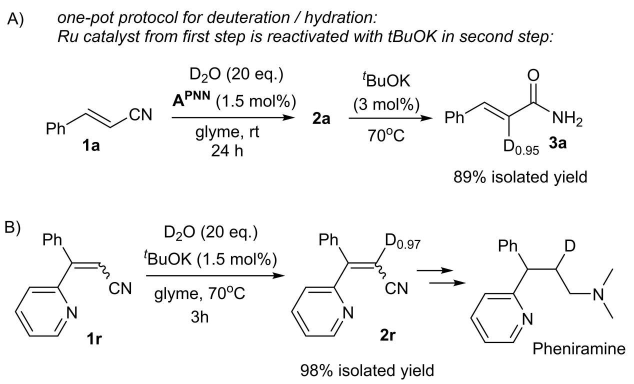
Subsequently, we evaluated the use of Ru-catalysis for the one-pot preparation of α-deuterated unsaturated amides by consecutive deuteration and hydration reactions.[20] As described above, A^{PNN} is unable to catalyse H/D exchange between D_2O and cinnamide (the product of nitrile hydration). It should be noted also that ^{t}BuOK alone does not catalyse nitrile hydration, and the Ru catalyst is needed for the second step. Thus we resorted to a protocol to first obtain deuterated nitrile **2a** and then convert this in a subsequent step to α-deuterated cinnamide. Although catalyst A^{PNN} is in principle able to perform both reactions, it was found to show poor activity for nitrile hydration at 70 °C after H/D exchange to **2a** for 24 hours at room temperature. However, we found that the deactivated Ru catalyst after the first step may be re-activated by the addition of 2 additional equivalents of ^{t}BuOK (3 mol%), and deuterated amide **3a** was obtained in 89% isolated yield in a straightforward manner (Scheme 3A).

The utility of this chemistry for the synthesis of a deuterated drug was demonstrated using an *E*/*Z* mixture (62/38) of 3-phenyl-3-(pyridin-2-yl) acrylonitrile **1r**, which was prepared via Horner-Wadsworth-Emmons chemistry. Compound **1r** is a precursor to the antihistamine Pheniramine (Avil), and representative of the 3,3-diarylacrylonitrile motif present in tubulin polymerization inhibitors (anticancer).[13,14] H/D exchange using our *t*BuOK-catalysed method resulted in virtually complete α-deuteration (97% D) of **1r** in just 3 hours (Scheme 3B). Product

Table 3. Substrate scope for Ru-catalysed selective α-deuteration of nitriles with D_2O.[a]



[a] Reaction was carried out with 0.25 mmol nitrile in 0.5 ml solvent, and deuteration level determined by ^{1}H NMR with solvent suppression.
[b] Extra base (3 mol%) was added.
[c] Reaction was run at 70 °C in THF.



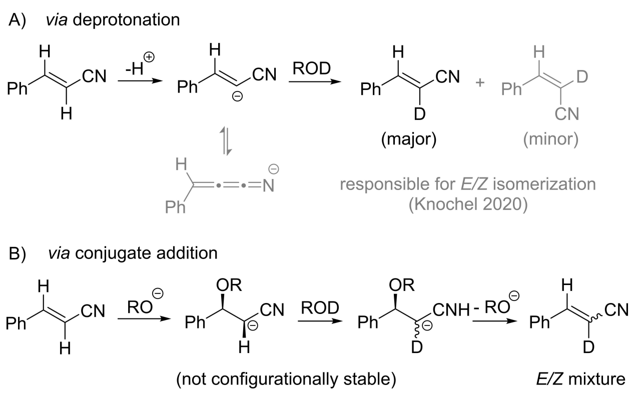
Scheme 3. Synthesis of deuterium-labelled cinnamide **3a** and pheniramine.

2 r is a precursor to Pheniramine via hydrogenation as reported in the literature.[21]

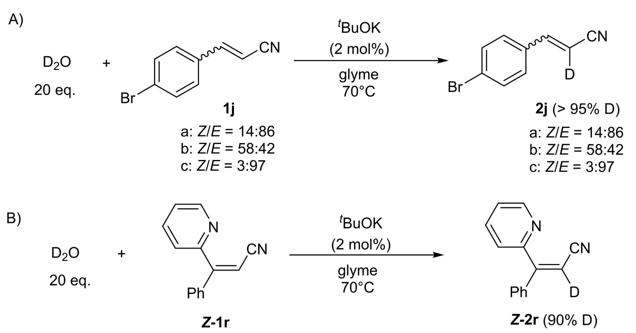
Mechanistic considerations. Regarding potential mechanisms for the H/D exchange reactions, two general pathways were considered: *i*) deprotonation of the unsaturated nitrile substrate at the α-C(sp^2)-H position to give a vinyl anion intermediate, followed by D^+ transfer from D_2O (Scheme 4A), or *ii*) reverrsible conjugate addition/elimination of alkoxide or hydroxide combined with D^+ transfer (Scheme 4B). The former pathway has been proposed by Feit et al. based on reactions between cinnamonitrile and (super) stoichiometric amounts of LDA as a strong base, followed by quenching with deuterated alcohols.[11] In Feit's work, some *E*/*Z* isomerization was observed and ascribed to a (slower) conjugate addition/elimination pathway,[11a] and later studies suggested that *E*/*Z* isomerization may result from configurational instability of vinyl anions, which is dependent on solvent polarity.[11b] Recently, Knochel and co-workers described the deprotonation of cinnamonitriles in continuous flow using the strong sodium base NaN^iPr_2 and subsequent quenching with electrophiles, where it was suggested that equilibration of the sodiated acrylonitrile to the corresponding cummulene could account for *cis*/*trans*-isomerization (Scheme 4A) for reactions with sterically hindered electrophiles.[22] It should be noted that a stoichiometric amount of base was used in Knochel's work. α-Selective catalytic H/D exchange at the vinyl group in styrenes has been reported by Bandar et al. via base-catalyzed addition of methanol using d_6-DMSO as deuterium source, which was proposed to operate via reversible conjugate addition of methanol.[17]

To shed some light on which pathways may be operative in our catalytic reactions, we started from *E*/*Z* isomer mixtures with different ratios, and evaluated how this ratio changed upon H/D exchange. Thus, the *para*-bromo substituted cinnamonitrile **1 j** was synthesized using Horner–Wadsworth-Emmons reaction, which afforded an 86/14 mixture of isomers (*E*/*Z*). Crystallization afforded a batch that was predominantly *E*-**1 j** (*E*/*Z* = 97/3), and workup of the mother liquor gave a batch of **1 j** enriched in the *Z*-isomer (*E*/*Z* = 42/58). Catalytic H/D exchange was studied with all three batches of **1 j** using 2 mol% of ^{t}BuOK as catalyst at 70 °C in glyme (Scheme 5). In all cases, high levels of H/D exchange were obtained (> 95%) after already 30 min, but no isomerization was observed. In addition, compound **1 r** was purified to the *Z*-isomer (> 99%), and tested in the ^{t}BuOK-catalysed deuteration (1 h at 70 °C) which resulted in 90% deuterium incorporation, and also no isomerization. These results are in agreement with path A, with D^+ transfer to the vinyl anion intermediate kinetically outcompeting the *E*/*Z* isomerization.[22]

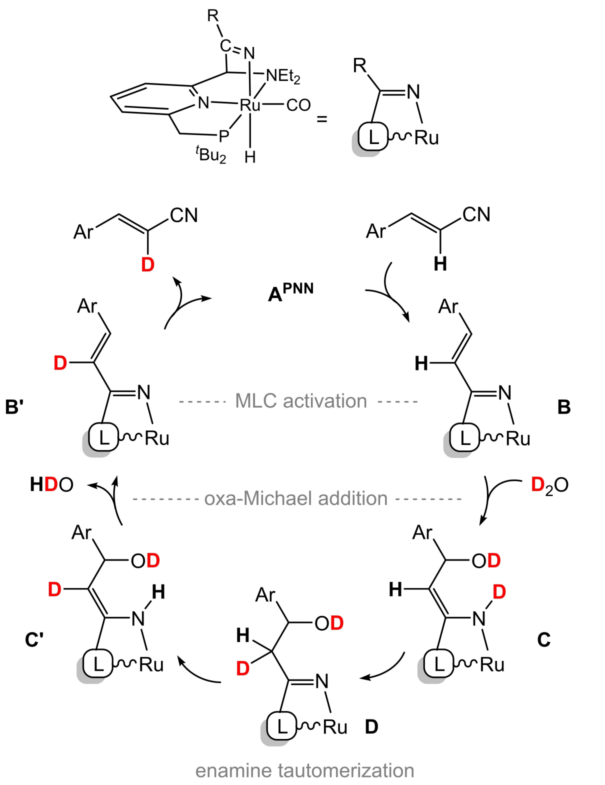
Similar to reactions catalysed by ^{t}BuOK, H/D exchange with substrates **1 j**/**1 r** using the Ru catalyst $\mathbf{A^{PNN}}$ did not lead to a change in the *E*/*Z* isomer ratios. However, as shown in Figure 2 the H/D exchange using $\mathbf{A^{PNN}}$ is found to be significantly faster than with ^{t}BuOK under identical conditions. Since $\mathbf{A^{PNN}}$ is a much weaker base than ^{t}BuOK,[23,24] this observation is not consistent with the deprotonation pathway for the Ru catalyst. The divergent reactivity of the electron-rich *p*-NMe_2 substituted cinnamonitrile (**1 e**), which does not undergo ^{t}BuOK-catalysed H/D exchange but is deuterated using $\mathbf{A^{PNN}}$ (*vide supra*), also suggests the two catalysts to operate via a different mechanism. Based on our work on nitrile activation using $\mathbf{A^{PNN}}$,[18,19,25] we propose that metal-ligand cooperative activation of the nitrile to generate a more reactive electrophile is responsible for the high catalytic activity of $\mathbf{A^{PNN}}$. A possible catalytic cycle is shown in Scheme 6. According to this proposal, conjugate addition of D_2O to intermediate **B** proceeds in a concerted manner as described previously to form the enamido species **C**.[18a] Tautomerization of **C** to the corresponding imido-Ru complex **D** places the deuterium atom at the α-C as required for H/D exchange. The reversibility of this tautomerization ensures that



Scheme 4. Potential mechanisms for H/D exchange in cinnamonitriles.



Scheme 5. ^{t}BuOK-catalysed deuteration of (A) **1 j** (with different *E*/*Z* ratios) and (B) *Z*-**1 r**.



Scheme 6. Proposed mechanism for the H/D exchange reaction catalysed by **A**^{PNN}.

the C(*H*)(*D*)-C=N fragment in **D** can revert by transfer of either H or D (to form **C** and **C'**, respectively). Concerted elimination of HDO from **C'** returns the α,β-unsaturated motif with *retention* of the stereochemistry around the C=C bond.

Conclusion

In summary, we demonstrated highly selective H/D exchange at the C(sp^2)-H bond at the α-position of cinnamonitrile derivatives using cheap and readily available D_2O as the deuterium source. The reaction is found to be catalysed by a strong Brønsted base (^{t}BuOK), but this is only efficient at elevated temperature (70 °C). In addition, a mild protocol was devised using Milstein's metal-ligand cooperative Ru PNN pincer complex, which allows the reaction to be run at room temperature in the absence of additional base. The prospect of this chemistry for pharmacological applications, where selective deuteration is useful to modify metabolic stability and other properties, is demonstrated by the synthesis of a deuterated precursor to Pheniramine. Based on the difference in rate between ^{t}BuOK- and **A**^{PNN}-catalyzed reactions, we propose that the Ru pincer catalysis involves metal-ligand cooperation to enable rapid, reversible conjugate addition of D_2O to the unsaturated nitriles.

Experimental Section

Catalysis experiments were carried out under nitrogen atmosphere by standard Schlenk line or glovebox techniques, using solvents/chemicals that were purified and dried as specified in the Supporting Information. Catalyst stock solutions were prepared and stored in the glovebox, either at room temperature (^{t}BuOK in glyme) or at −32 °C (**A**^{PNN} in toluene). Catalysis using ^{t}BuOK was typically carried out using 0.25 mmol of substrate in a J. Young's NMR tube containing a solution of D_2O (20 equiv.) in glyme. The NMR tube was heated to 70 °C outside the glovebox, and the extent of deuteration was monitored by NMR spectroscopy. For reactions catalysed by **A**^{PNN}, the toluene stock solution was evaporated and the residue taken up into glyme, after which it was added to the substrate in a J. Young's NMR tube containing D_2O (20 equiv) in glyme. After completion of the reaction (ca. 95% deuteration), the mixture was cooled down to room temperature. Subsequently, the reaction mixture was exposed to air to deactivate the catalyst, and all volatiles were removed under reduced pressure. The residue was redissolved in dichloromethane and purified either by column chromatography or by filtration over a simple plug of silica to give the desired product after evaporation of the solvent.

Synthesis of *2-(^{2}H)*cinnamonitrile (**2 a**) on gram-scale: A solution of 1.29 g of **1 a** (10 mmol) was dissolved in 20 mL of glyme. To this was added 4.0 g of D_2O (200 mmol) and 22.4 mg of ^{t}BuOK (0.2 mmol), after which the mixture was heated to 70 °C for 5 h. After removal of volatiles, the residue was purified by column chromatography on silica (dichloromethane eluent), which afforded 1.26 g of product (9.69 mmol) that contained ca. 97% of deuterium at the α-position based on ^{1}H NMR integration. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.50–7.31 (m, 6H, Ph and PhC**H**), 5.88 (d, J = 16.7 Hz, 0.03H, C**H**CN). ^{13}C NMR (101 MHz, chloroform-*d*) δ 150.6 and 150.6 (Ph**C**H), 133.6(1-Ph), 131.3, 129.2 and 127.4 (*ortho, meta, para*-Ph), 118.22 (**C**N), 96.4 (**C**HCN), 96.2 (t, J = 26.2 Hz **C**DCN). HRMS (ESI) calcd. for C_9H_6DN [M + H$^+$] 131.07140, found 131.07131. Elemental Analysis for C_9H_6DN: Calculated: C, 83.69; H + D, 5.46; N, 10.84; Found: C, 83.34; H + D, 5.50; N, 10.71.

Synthesis of tert-butyl-4-(2-(^{2}H)2-cyanovinyl)benzoate (**2 p**): In the glovebox, 0.41 mL of a 7.5 mmol/L stock solution of **A**^{PNN} catalyst (0.003 mmol, 1.5 mol%) was added to a 20 mL vial. After removal of all volatiles under vacuum, 4.1 ml of glyme was added to dissolve the catalyst again. After ca. 2 min, D_2O (74 µl, 4.1 mmol, 20 eq.) was added to the catalyst solution, and then the mixture was transferred into a GC vial (equipped with a Teflon-lined screw cap and additionally sealed with parafilm) containing **1 p** (47 mg, 0.205 mmol, 1 eq.). The reaction mixture was taken out of the glovebox and stirred at room temperature for 1.5 h. Then the reaction was exposed to air to deactivate the catalyst. After removal of all volatiles under reduced pressure, the residue was redissolved in dichloromethane and purified through a simple plug of silica to give the desired product as a white solid in 91% yield (43.0 mg, 0.187 mmol). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.04 (d, J = 8.4 Hz, 0.69H, *cis-meta*-Ph), 8.00 (d, J = 8.4 Hz, 1.29H, *trans-meta*-Ph), 7.82 (d, J = 8.3 Hz, 0.72H, *cis- ortho*-Ph), 7.48 (d, J = 8.3 Hz, 1.32H, *trans-ortho*-Ph), 7.41 (s, 0.61H, *trans*-C**H**CD), 7.17 (s, 0.34H, *cis*-CHCD), 5.96 (d, $J=16.7$ Hz, 0.03H, *trans*-CHCN), 5.55 (d, $J=12.1$ Hz, 0.02H, *cis*-CHCN), 1.59 (s, 3.8H,tBu), 1.59 (s, 5.7H, tBu). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 164.9 and 164.8 (**C**=O), 149.5 and 149.4 (**C**HCD), 137.1 and 137.0 (4-Ph), 134.3 and 134.0 (1-Ph), 130.2 and 130.0 (*meta*-Ph), 128.8 and 127.2(*ortho*-Ph), 117.8 and 117.0 (**C**N), 98.6 (*trans*-**C**HCN), 98.4 (t, $J=26.1$ Hz, *trans*-**C**DCN), 97.3 (*cis*-**C**HCN), 97.1(t, $J=26.7$ Hz, *cis*-**C**DCN), 81.8 and 81.7 (**C**(CH$_3$)$_3$), 28.2 (C(**C**H$_3$)$_3$). HRMS (ESI) calcd. for $C_{14}H_{14}DNO_2$ [M+H$^+$] 231.12383, found 231.12366.

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