Selective α-Deuteration of Cinnamonitriles using D$_2$O as Deuterium Source
Guo, Beibei; de Vries, Johannes G.; Otten, Edwin

Published in:
Advanced Synthesis and Catalysis

DOI:
10.1002/adsc.202101093

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2022

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment.

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.
Pushing the boundaries of chemistry?
It takes #HumanChemistry

Make your curiosity and talent as a chemist matter to the world with a specialty chemicals leader. Together, we combine cutting-edge science with engineering expertise to create solutions that answer real-world problems. Find out how our approach to technology creates more opportunities for growth, and see what chemistry can do for you at:

evonik.com/career
Selective α-Deuteration of Cinnaminitriles using D\textsubscript{2}O as Deuterium Source

Beibei Guo,\textsuperscript{a} Johannes G. de Vries,\textsuperscript{b,*} and Edwin Otten\textsuperscript{a,*}

\textsuperscript{a} Stratingh Institute for Chemistry
University of Groningen
Nijenborgh 4
9747 AG Groningen, The Netherlands
E-mail: edwin.otten@rug.nl

\textsuperscript{b} Leibniz Institute für Katalyse e. V.
Albert-Einstein-Strasse 29a
18059 Rostock, Germany
E-mail: johannes.devries@catalysis.de

Manuscript received: September 3, 2021; Revised manuscript received: September 24, 2021; Version of record online: October 8, 2021

Supporting information for this article is available on the WWW under https://doi.org/10.1002/adsc.202101093

© 2021 The Authors. Advanced Synthesis & Catalysis published by Wiley-VCH GmbH. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

Abstract: The selective α-deuteration of α,β-unsaturated nitriles using the strong base 'BuOK or a metal-ligand cooperative Ru pincer catalyst is described. With D\textsubscript{2}O as deuterium source and glyme as solvent at 70 °C, 'BuOK is an efficient catalyst for deuteration at the α-C(sp\textsuperscript{2}) position of cinnaminitriles, providing access to a broad range of deuterated derivatives in good to excellent yields and with very high levels of deuteration incorporation. While the 'BuOK-catalysed protocol does not tolerate base-sensitive functional groups, cinnaminitrile 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 'BuOK, allowing reactions to proceed well even at room temperature. A mechanistic proposal is put forward that involves deprotonation of the cinnaminitrile α-CH position when using 'BuOK as catalyst, whereas H/D exchange catalysis with the Ru PNN pincer likely proceeds via (reversible) oxa-Michael addition of D\textsubscript{2}O.

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

Introduction

Isotopically labelled compounds in which one or more hydrogen (\textsuperscript{1}H) atoms are substituted for the heavier isotopes deuterium (\textsuperscript{2}H or D) or tritium (\textsuperscript{3}H 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).\textsuperscript{[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.\textsuperscript{[2]} Drugs that are deuterated in selected positions can have substantially altered pharmacokinetics and metabolic stability,\textsuperscript{[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\textsubscript{3} groups, by the U.S. Food and Drug Administration (FDA) as the first deuterium-containing drug presents an important milestone,\textsuperscript{[4]} and many more deuterated drug candidates are in clinical trials.\textsuperscript{[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\textsubscript{2}O or D\textsubscript{3} 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, 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), whereas the C–H bond next to the nitrile moiety is sufficiently acidic to exchange with D₂O under mild conditions (Scheme 1b). The latter reaction was reported as early as 1957 using base catalysis, and more recently Gunanathan reported efficient Ru catalysts based on an aliphatic PNP pincer scaffold for the α-deuteration of saturated aliphatic nitriles. 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, the catalytic deuteration of the sp²-carbons of unsaturated nitriles has remained underdeveloped.

In 1963, Hauser and co-workers reported that trans-cinnaminitrile 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%).

The group of Feit developed the chemistry of mono- and dilithiated cinnaminitriles, and demonstrated α-monodeuteration as well as α,β-dideuteration using LDA/MeOD, 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-deuteronated cinnaminitrile with >95% deuterium incorporation.

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. We hypothesised that our protocol for oxa-Michael additions to α,β-unsaturated nitriles using a metal-ligand cooperative Ru pincer catalyst could similarly lead to selective α-deuteration under conditions where conjugate addition is fast yet thermodynamically unfavourable. The use of D₂O 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, 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 cinnaminitrile 1a, using 1.5 mol% of the metal-ligand cooperative Ru PNN pincer catalyst A^PNN (structure shown in Table 1). Conducting the reaction at 0.25 mmol scale in d₈-THF solvent (0.5 mL) with 5 mmol D₂O, 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 ¹H NMR spectra in d₈-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...
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 \( \alpha \)-position in the presence of a catalytic amount of \( \text{A}^\text{PNN} \). No H/D exchange was observed in the absence of \( \text{A}^\text{PNN} \). The related PNP-pincer catalyst \( \text{A}^\text{PNP} \) 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 \( \text{A}^\text{PNP} \) is active for both H/D exchange and nitrile hydration.

The deuterated amide is obtained due to hydration of \( \text{d}^1 \)-cinnamonitrile (2a), rather than H/D exchange of the amide: control experiments with cinnamide/D\( \text{D}_2 \)O did not result in deuteration at the CH bonds.

A screening of different solvents with \( \text{A}^\text{PNN} \) as catalyst gave very similar results for relatively non-polar solvents such as toluene and MTBE, 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 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\( \text{D}_2 \)O relative to cinnamonitrile). Subsequent experiments thus used glyme as the solvent of choice.

To confirm the role of the Ru-complex \( \text{A}^\text{PNN} \) 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 Bronsted bases KOH and \( \text{tBuOK} \) 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 \( \text{tBuOK} \) 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 \( \alpha \)-deuteration level of cinnamonitrile \( 1\text{a} \) (92%) also when using \( \text{tBuOK} \) as catalyst, even after only 5 hours (entry 9 in Table 1). For comparison, the reaction 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\( \text{D}_2 \)O relative to cinnamonitrile). Subsequent experiments thus used glyme as the solvent of choice.

Monitoring the deuteration in glyme by \( ^1\text{H} \) 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).

Table 1. Optimization of H/D exchange at the \( \alpha \)-position of cinnamonitrile \( 1\text{a} \) with D\( \text{D}_2 \)O.\(^{[a]}\)

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>cat (mol%)</th>
<th>temp (°C)</th>
<th>deuteration (%)(^{[b]})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{d}_8 )-THF</td>
<td>( \text{A}^\text{PNN} ) (1.5)</td>
<td>rt</td>
<td>37</td>
</tr>
<tr>
<td>2</td>
<td>( \text{d}_8 )-THF</td>
<td>( \text{A}^\text{PNP} ) (1.5)</td>
<td>rt</td>
<td>1\text{a}2\text{a} + amide</td>
</tr>
<tr>
<td>3</td>
<td>toluene</td>
<td>( \text{A}^\text{PNN} ) (1.5)</td>
<td>rt</td>
<td>39</td>
</tr>
<tr>
<td>4(^{[c]})</td>
<td>MTBE</td>
<td>( \text{A}^\text{PNN} ) (1.5)</td>
<td>rt</td>
<td>36</td>
</tr>
<tr>
<td>5(^{[d]})</td>
<td>DCE</td>
<td>( \text{A}^\text{PNN} ) (1.5)</td>
<td>rt</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>1,4-dioxane</td>
<td>( \text{A}^\text{PNN} ) (1.5)</td>
<td>rt</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>glyme</td>
<td>( \text{A}^\text{PNN} ) (1.5)</td>
<td>rt</td>
<td>95</td>
</tr>
<tr>
<td>8</td>
<td>glyme</td>
<td>( \text{tBuOK} ) (2)</td>
<td>rt</td>
<td>32</td>
</tr>
<tr>
<td>9(^{[e]})</td>
<td>glyme</td>
<td>( \text{tBuOK} ) (2)</td>
<td>70</td>
<td>92</td>
</tr>
</tbody>
</table>

\(^{[a]}\) Reaction conditions: cinnamonitrile (0.25 mmol), D\( \text{D}_2 \)O (5 mmol) and catalyst in 0.5 mL of solvent, N\(_2\) atmosphere, 1 day.

\(^{[b]}\) Degree of deuteration was determined by \( ^1\text{H} \) NMR spectroscopy.

\(^{[c]}\) MTBE, methyl tert-butyl ether.

\(^{[d]}\) DCE, 1,2-dichloroethane.

\(^{[e]}\) Reaction time of 5 hours.

Figure 1. \( ^1\text{H} \) NMR spectra of \( \text{A}^\text{PNN} \)-catalysed H/D exchange of trans-cinnamonitrile (1\text{a}) with D\( \text{D}_2 \)O in \( \text{d}_8 \)-THF at room temperature. Spectra are taken after 9 h (bottom), 24 h (middle) and 48 h (top).
profiles for H/D exchange using both APNN and tBuOK are shown in Figure 2, highlighting that the Ru-catalyst APNN shows superior performance in H/D exchange compared to tBuOK when carried out at room temperature, but tBuOK becomes competitive at elevated temperature.

It is worth to mention that both APNN- and tBuOK-catalysed reactions yield the α-deuterated product 2a exclusively: 1H NMR integration as well as the lack of C–D coupling in the 13C(1H) 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 tBuOK.** The substrate scope of tBuOK-catalysed H/D-exchange was investigated. The reactions were conducted at 70 °C in glyme solvent, with 20 equiv. of D2O as deuterium source and using 2 mol% of catalyst. As shown in Table 2, cinnamionitrile derivatives with electron-donating substituents (1b, p-Me; 1c, p-OMe; 1d, p,m-(OMe)2) were less efficiently deuterated than the parent cinnamionitrile 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 tBuOK 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-Me2N 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% tBuOK), but in this case an increase in catalyst loading to 10 mol% restored activity and afforded a high degree of deuteration (92%; entry 10).

![Figure 2. Conversion vs. time plot for H/D exchange of cinnamionitrile (1a) with D2O in glyme [Ru = A^NN].](image)

| Table 2. Substrate scope of tBuOK-catalysed selective α-deuteration of nitriles with D2O.[a] |
|---|---|---|---|---|---|
| D2O + R2C=CNR | R2C=CND R2Cu (2 mol%) glyme, 70°C | entry | compound | R1 | R2 | time (h) | D% | yield (%) |
| 1b | 1a | Ph | H | 5 | 95(>99) | 94 | 1c |
| 2c | 1a | Ph | H | 5 | 98 | 97 | 2d |
| 3 | 1b | p-Me-Ph | H | 6 | 24 | nd | 4d |
| 4c | 1b | p-Me-Ph | H | 5 | 94 | 89 | 5 |
| 5 | 1c | p-OMe-Ph | H | 6 | 68 | nd | 6d |
| 6d | 1c | p-OMe-Ph | H | 6.7 | 91 | 96 | 7 |
| 7 | 1d | p,m-(OMe)2-Ph | H | 6 | 68 | nd | 8 |
| 8d | 1d | p,m-(OMe)2-Ph | H | 2.8 | 92 | 86 | 9c |
| 9c | 1e | p,NMe2-Ph | H | - | - | - | 10c |
| 10c | 1f | p-F-Ph | H | 2.8 | 92 | 89 | 11 |
| 11 | 1g | o-Cl-Ph | H | 0.75 | 97 | 92 | 12 |
| 12 | 1h | m-Cl-Ph | H | 0.75 | 96 | 91 | 13 |
| 13 | 1i | p-Cl-Ph | H | 0.75 | 96 | 93 | 14 |
| 14 | 1j | p-Br-Ph | H | 0.75 | 95 | 90 | 15 |
| 15 | 1k | 2-Py | H | 1 | 97 | 86 | 16 |
| 16 | 1l | 2-furyl | H | 3 | 95 | 83 | 17 |
| 17 | 1m | 2-thienyl | H | 1 | 96 | 90 | 18 |
| 18 | 1n | Ph | Ph | 4.25 | 91 | 97 | 19 |
| 19 | 1o | p-F-Ph | Cl | - | - | - |

[a] Reactions were carried out with 0.25 mmol nitrile in 0.5 ml solvent, and deuterium determined by 1H NMR with solvent suppression.
[b] >99% deuterium labelling was obtained by a second run with addition of fresh solvent, D2O 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 BuOK in only 45 min. Unsubstituted 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-deut erated products in high isolated yield and with excellent levels of deuteriation (entries 15-17). The β-disubstituted substrate 3,3-dipheny lacrylonitrile (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 chloro-3-(4-fluorophenyl) acrylonitrile (the product of nitrile hydration). It should be noted also that ‘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 ‘BuOK (3 mol%), and deuterated amide 3a was obtained in 89% isolated yield in a straightforward manner (Scheme 3A).

Subsequently, we evaluated the use of Ru-catalysis for the one-pot preparation of α-deuterated unsaturated amides by consecutive deuteration and hydration reactions. As described above, A_PNN is unable to catalyse H/D exchange between D_2O and cinnamide (the product of nitrile hydration). 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-Wads worth-Emmons chemistry. Compound 1r is a precursor to the antihistamine Pheniramine (Avil), and representative of the 3,3-diacylacrylonitrile motif present in tubulin polymerization inhibitors (anticancer). H/D exchange using our rBuOK-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. 

<table>
<thead>
<tr>
<th>D_2O</th>
<th>A_PNN (1.5 mol%)</th>
<th>H/C</th>
<th>α-deuterated product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-CN</td>
<td>A_PNN (1.5 mol%)</td>
<td>H/C</td>
<td>CN</td>
<td></td>
</tr>
<tr>
<td>2p</td>
<td>1.5 h, 91% yield</td>
<td></td>
<td>CN</td>
<td></td>
</tr>
<tr>
<td>2q</td>
<td>2 h, 86% yield</td>
<td></td>
<td>CN</td>
<td></td>
</tr>
<tr>
<td>2a</td>
<td>24 h, 92% yield</td>
<td></td>
<td>CN</td>
<td></td>
</tr>
<tr>
<td>2f</td>
<td>24 h, 92% yield</td>
<td></td>
<td>CN</td>
<td></td>
</tr>
</tbody>
</table>

[a] Reaction was carried out with 0.25 mmol nitrile in 0.5 ml solvent, and deuteration level determined by 1H 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.
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(sp²) position to give a vinyl anion intermediate, followed by D⁺ transfer from D₂O (Scheme 4A), or ii) reversible 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 cinnaminitrile and (super) stoichiometric amounts of LDA as a strong base, whereas the latter was described by Horner–Wadsworth-Emmons reaction, using d₆-DMSO as deuterium source, which was kinetically outcompeting the E/Z isomerization.

 Recently, Knochel and co-workers described the deprotonation of cinnaminitriles in continuous flow using the strong sodium base NaN₅Pr₂ and subsequent quenching with alkoxides, where it was suggested that equilibrium of the sodiated acrylonitrile to the corresponding cumulene could account for cis/trans-isomerization (Scheme 4A) for reactions with sterically hindered electrophiles. 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 Knochel’s work. α-Selective catalytic H/D exchange at the α-C(sp²) position to give a vinyl anion intermediate, followed by D⁺ transfer from D₂O (Scheme 4A), or ii) reversible 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 cinnaminitrile and (super) stoichiometric amounts of LDA as a strong base, followed by quenching with deuterated alcohols. In Feit’s work, some E/Z isomerization was observed and ascribed to a (slower) conjugate addition/elimination pathway, and later studies suggested that E/Z isomerization may result from configurational instability of vinyl anions, which is dependent on solvent polarity. Recently, Knochel and co-workers described the deprotonation of cinnaminitriles in continuous flow using the strong sodium base NaN₅Pr₂ and subsequent quenching with electrophiles, where it was suggested that equilibration of the sodiated acrylonitrile to the corresponding cumulene could account for cis/trans-isomerization (Scheme 4A) for reactions with sterically hindered electrophiles. 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 d₆-DMSO as deuterium source, which was proposed to operate via reversible conjugate addition of methanol.

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 cinnaminitrile 1j 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-1j (E/Z = 97/3), and workup of the mother liquor gave a batch of 1j enriched in the Z-isomer (E/Z = 42/58). Catalytic H/D exchange was studied with all three batches of 1j using 2 mol% of '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 1r was purified to the Z-isomer (>99%), and tested in the '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.

Similar to reactions catalysed by 'BuOK, H/D exchange with substrates 1j/1r using the Ru catalyst A⁵⁷⁶ did not lead to a change in the E/Z isomer ratios. However, as shown in Figure 2 the H/D exchange using A⁵⁷⁶ is found to be significantly faster than with 'BuOK under identical conditions. Since A⁵⁷⁶ is a much weaker base than 'BuOK, this observation is not consistent with the deprotonation pathway for the Ru catalyst. The divergent reactivity of the electron-rich p-NMe₂ substituted cinnaminitrile (1e), which does not undergo 'BuOK-catalysed H/D exchange but is deuterated using A⁵⁶⁷ (vide supra), also suggests the two catalysts to operate via a different mechanism. Based on our work on nitrile activation using A⁵⁶⁷, we propose that metal-ligand cooperative activation of the nitrile to generate a more reactive electrophile is responsible for the high catalytic activity of A⁵⁶⁷. A possible catalytic cycle is shown in Scheme 6. According to this proposal, conjugate addition of D₂O to intermediate B proceeds in a concerted manner as described previously to form the enamido species C, which then tautomerizes 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
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(sp²)-H bond at the α-position of cinnamonitrile derivatives using cheap and readily available D₂O as the deuterium source. The reaction is found to be catalysed by a strong Brønsted base (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 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 BuOK- and A²PNN-catalyzed reactions, we propose that the Ru pincer catalysis involves metal-ligand cooperation to enable rapid, reversible conjugate addition of D₂O 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 (BuOK in glime) or at −32°C (A²PNN in toluene). Catalysis using BuOK was typically carried out using 0.25 mmol of substrate in a J. Young’s NMR tube containing a solution of D₂O (20 equiv.) in glime. 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 A²PNN, the toluene stock solution was evaporated and the residue taken up into glime, after which it was added to the substrate in a J. Young’s NMR tube containing D₂O (20 equiv.) in glime. 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-(1H)cinnamonitrile (2a) on gram-scale: A solution of 1.29 g of 1a (10 mmol) was dissolved in 20 mL of glime. To this was added 4.0 g of D₂O (200 mmol) and 22.4 mg of 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) and then co-evaporated with toluene and D₂O (200 mmol), before being added to the substrate in a J. Young’s NMR tube containing D₂O (20 equiv.) in glime. 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 tert-butyl-4-(2-(1H)cyano vinyl)benzoate (2p): In the glovebox, 0.41 mL of a 7.5 mmol/L stock solution of A²PNN 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 glime was added to dissolve the catalyst again. After ca. 2 min, D₂O (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 1p (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).

© 2021 The Authors. Advanced Synthesis & Catalysis published by Wiley-VCH GmbH
Acknowledgements

Financial support from the Netherlands Organisation for Scientific Research (NWO) (VIDI grant to EO) and the China Scholarship Council (grant to BG) is gratefully acknowledged.

References

[24] Deprotonation of 1a by the ruthenium catalyst A²⁺⁺⁺ is calculated to be highly endergonic (ΔG = +23.5 kcal/mol) using density functional theory (TPSS/Def2TZVP level of theory including SMD solvation model and dispersion correction).