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The reductive deaminative conversion of nitriles to alcohols using *para*-formaldehyde in aqueous solution†

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We report herein, for the first time, the application of *para*-formaldehyde (pFA) to the reductive deamination of both aliphatic and aromatic nitriles in aqueous solution under transfer hydrogenation conditions. A broad range of primary alcohols have been synthesized selectively with very good to excellent yields under the optimized conditions. The study disclosed that the air-stable, inexpensive and commercially available catalyst [Ru(*p*-cymene)Cl₂]₂ acts as the catalyst precursor in this reaction, converting to other more active catalytic species in the presence of pFA, resulting in its degradation to CO₂ and H₂. Nitriles are also showed to play a dual role in this transformation, both as a substrate and as a ligand, where the dimeric catalyst structures convert to monomeric ones upon the coordination of nitrile molecules.

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Introduction

Hydrogenation is among the most important chemical reactions, at all stages, from laboratory to industry, in order for the synthesis of high value products from unsaturated organic molecules. Traditional methods including the use of main group metal hydrides such as LiAlH₄ and NaBH₄ have received less attention recently as their application is accompanied by the use of harsh reaction conditions, low yields and poor selectivity.^{1,2} The use of pressurized hydrogen is also not favoured due to the safety problems and environmental concerns as well as the expense and inconvenience of working with gaseous H₂, especially from the industrial point of view. Transfer hydrogenation (TH), on the other hand, has emerged as a powerful alternative with lots of advantages including milder reaction conditions, easier operational setup, more selectivity and reduced flammability compared to direct hydrogenation using pressurized hydrogen gas.^{3–5} With the aid of TH, various easily available and safe to handle hydrogen donating molecules can be used as the hydrogen source instead of molecular dihydrogen in the presence of a transition metal-based catalyst to activate both substrate and the hydrogen source in this reaction. Organometallic complexes of ruthenium as well as Ru nanoparticles are among the most

frequently used catalysts in this transformation. Also the use of abundant metals such as Fe,^{6–8} Co,⁹ and Mn (ref. 10) PNP and NNP pincers and phosphino complexes¹¹ has been reported more recently. However, most of these catalytic systems are still rather expensive, owing to the ligand backbone which surpasses the costs of the central metal. Moreover, they are air and moisture sensitive and often not commercially available and therefore it requires a synthesis under inert conditions. All these factors make the whole system more complicated and less sustainable. Therefore, considering the increasing interest in developing more sustainable synthetic methods, finding a catalytic system which does not suffer from these drawbacks and can work under milder reaction conditions means that TH reactions are very beneficial and of great importance.

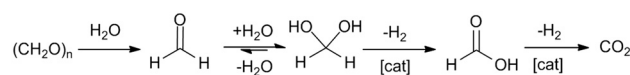
As previously mentioned, different organic and inorganic molecules have been employed as the hydrogen resource in TH and so far these have included alcohols,^{12–16} boranes,^{17–19} Hantzsch ester,²⁰ and formates,^{21,22} among others.^{23,24}

Recently, this group has reported the selective and mild generation of H₂ from formaldehyde in aqueous solution which can also be generated *in situ* from *para*-formaldehyde (pFA) or methanol in the presence of a [Ru(*p*-cymene)Cl₂]₂ dimer; a reaction which produces CO₂ as the only by-product (Scheme 1).^{16,25–28} It has also been shown that methanol can be used as a H₂ source for TH in a chemoenzymatic

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Scheme 1 The sequence of the catalysed H₂ generation steps of the pFA/water system.²⁸

conversion for the reduction of alkenes which cannot be reduced by enzymes.¹⁶

Formaldehyde is an inexpensive and readily available C1 building block which is produced annually in the range of 30 million tons,²⁵ because many industries use formaldehyde for the production of daily commodities.²⁶ It also has great potential for use as a liquid organic hydrogen carrier (LOHC) molecule for a future hydrogen economy based on C1-molecules.²⁵ Although the hydrogen content of aqueous formaldehyde is 8.4 wt% because the equilibrium favours methanediol, which is lower than in methanol (12.5 wt%), and from the thermodynamic point of view, H₂ production from aqueous formaldehyde is more attractive because methanol reforming is endergonic and formaldehyde reforming is exergonic.^{25,29,30}

In continuation of previous research where it was demonstrated that on the one hand aqueous formaldehyde formed *in situ* can be used for TH of alkenes,¹⁶ and on the other hand nitriles had been converted selectively to primary amines and secondary imines,³¹ now the challenge to convert selectively, under TH conditions, nitriles into alcohols must be tackled. Examples for this deaminative transformation of nitriles are rare and usually the reduction has a poor selectivity giving a mixture of, for example, amine, imine, aldehyde and alcohol or the reaction stops at the aldehyde stage, or it requires harsh reaction conditions (Scheme 2) and sensitive/expensive catalysts.^{32–37}

In 2004, Li and co-workers reported the first selective conversion of nitriles to alcohols using a Ru-TPPTS catalyst (TPPTS = [P(*m*-C₆H₄SO₃Na)₃]) prepared *in situ* (Scheme 2a).³⁵

However, they needed to use TPPTS to stabilize and solubilize their catalyst which is an expensive ligand and makes the protocol less attractive. In addition, the application of 50 bar H₂ and 120 °C in this work can be considered as harsh reaction conditions. Most recently, Hashmi and co-workers also showed successful conversion of nitriles to primary alcohols in the presence of RuHCl(CO)(PPh₃)₃ as catalyst (Scheme 2b).³⁴

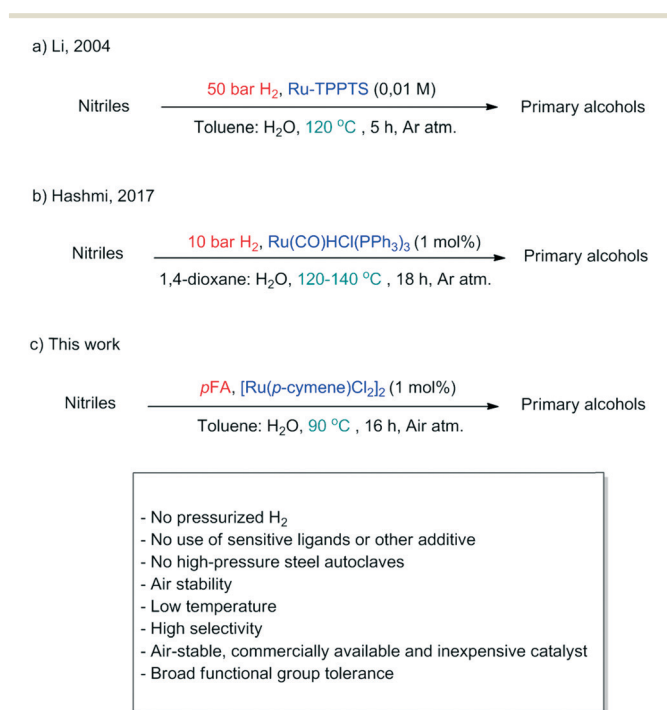
Again, despite obtaining good selectively, the reaction conditions are still quite harsh (10 bar H₂ in a 1 : 1 mixture of 1,4-dioxane:H₂O at 140 °C for 18 h). Also, these reactions need to be done under an inert atmosphere with use of a glovebox or Schlenk line to handle the chemicals under an argon atmosphere which increases the complexity of the reaction and decreases the chance for use in industrial applications. Therefore, selective conversion of aliphatic and aromatic nitriles to primary alcohols under mild, feasible and safe conditions, using an air-stable, inexpensive and commercially available catalyst is still the missing piece in the reductive deamination puzzle. Notably, the reverse reaction, the conversion of alcohols to nitriles is also possible with Ni-catalysts and ammonia.^{38,39}

Herein, considering all the previously mentioned limitations and to avoid using pressurized hydrogen, selective reductive deamination of both aliphatic and aromatic nitriles under mild conditions using pFA C1 source of TH in an aqueous system as shown in Scheme 2c, is reported first. The commercially available, air-stable and inexpensive Ru(*p*-cymene)Cl₂ dimer has been proved to be an active and appropriate catalyst for this transformation.

Results and discussion

Optimization of reaction conditions

As reduction of nitriles is normally a non-selective reaction which results in the formation of different by-products, from benzamide to imine and amines, it was necessary to find the best conditions which lead to the selective formation of the desired product. To this end, benzonitrile was selected as the benchmark substrate. As is already known from previous work, in order to produce hydrogen from pFA, the presence of water and catalyst in the reaction medium is necessary. Therefore, a combination of 1 mol% of Ru(*p*-cymene)Cl₂ dimer as catalyst and water as solvent at 120 °C was employed in the first attempt, and for the ratio of pFA to benzonitrile 10 : 1 was selected to be. It has been reported that benzonitrile can be hydrated in the presence of water and Ru-based catalysts to produce benzamide as the only product,⁴⁰ moreover it is known that the hydration of nitriles to amides can also be performed by base catalysis (NaOH) or acid catalysis.⁴¹ The challenge was to prevent the formation of this side product. As was expected, a mixture of benzyl alcohol to benzamide with the ratio of 1 : 6.8, was obtained under these conditions and no formation of amine or imine was detected in this case (Table 1, entry 1). To prevent the formation of benzamide, various organic solvents were added



Scheme 2 A comparison of previously reported selective conversions of nitriles to primary alcohols with the present work.

Table 1 Solvent screening

| $\text{PhCN} + 10 \text{ eq. pFA} \xrightarrow[\text{Solvent, 120}^\circ\text{C, 10 h}]{[\text{Ru}] (1 \text{ mol}\%)} \text{Ph-CH}_2\text{-OH} + \text{Ph-C(=O)-NH}_2$ <div style="display: flex; justify-content: space-around; width: 100%;"> 1 2 </div> | | |
|---|--|----------------------------|
| Entry | Solvent (ratio) | 1 : 2 ^a (ratio) |
| 1 | H ₂ O | 13 : 87 |
| 2 | H ₂ O : EtOH (1 : 1) | 43 : 57 |
| 3 | H ₂ O : i-PrOH (1 : 1) | 52 : 48 |
| 4 | H ₂ O : 1,4-dioxane (1 : 1) | 51 : 49 |
| 5 | H ₂ O : toluene (1 : 1) | 56.4 : 43.6 |
| 6 | H ₂ O : MeOH (1 : 1) | 45 : 55 |
| 7 | H ₂ O : toluene (1.5 : 2.5) | 57.2 : 42.8 |
| 8 | H ₂ O : toluene (2.5 : 1.5) | 38.5 : 61.5 |

Reaction conditions: benzonitrile (1 mmol), pFA, [Ru] = [Ru(*p*-cymene)Cl₂]₂, solvent (4 mL in total), 120 °C, 10 h. ^a NMR yield (hexamethyldisilane was used as an internal standard); ratio given at full conversion.

to the system to change the reaction medium. Addition of a second solvent improved the formation of benzyl alcohol to a large extent, while there was no sign of the formation of either amine nor imine as the other possible by-products (Table 1, entries 2–6). This is already a big step towards the selective synthesis of benzyl alcohol from benzonitrile as in most of the previously reported conditions, the formation of a mixture of all possible by-products had been unavoidable. This confirms that deaminative hydrogenation of nitriles using H₂ generated *in situ* from pFA was more selective compared to the use of pressurized H₂. According to the obtained results, although a mixture of toluene and water resulted in the highest ratio of benzyl alcohol to benzamide, other organic solvents, even methanol and ethanol, could also improve the selectivity (Table 1, entries 2, 6).

Observing the significant effect of the reaction medium on this transformation, the ratio of the solvents was changed in the next step. The best results were obtained using a ratio of 1:1 from toluene and water which was selected as the optimum solvent system (Table 1, entries 5, 7–8). It should be also mentioned that for reaction times of 30, 60 and 120 min product formation could not be observed which indicated that there was an induction period to form the active hydrogenation catalyst species.

Different bases were also added to the reaction to investigate the effect of pH on this transformation (Table 2, entries 1–3). Based on the results, benzamide was the major product in the presence of any organic or inorganic base in the medium. This observation was also not surprising as the conversion of nitrile to amide can be facilitated in basic media.⁴¹

2,2'-Bipyridine, 1,10-phenanthroline, triphenylphosphine and 1,2-bis(diphenylphosphino)ethane (dppe) were added next, to the reaction mixture to attempt to see if they improve the catalytic activity of the Ru catalyst (Table 2, entries 4–7). As a result, the nitrogen-based ligands did not change the outcome of the reaction although when using 1,10-phenanthroline, the reaction did not complete within 12 h.

Table 2 Base and ligand screening

| $\text{PhCN} + 10 \text{ eq. pFA} \xrightarrow[\text{H}_2\text{O:toluene (1:1), 120}^\circ\text{C, 10 h, +additives (base or ligand)}]{[\text{Ru}] (1 \text{ mol}\%)} \text{Ph-CH}_2\text{-OH} + \text{Ph-C(=O)-NH}_2$ <div style="display: flex; justify-content: space-around; width: 100%;"> 1 2 </div> | | |
|--|--------------------------------|----------------------------|
| Entry | Additive (base or ligand) | 1 : 2 ^a (ratio) |
| 1 | KO ^t Bu | 1 : 21 |
| 2 | K ₂ CO ₃ | 1 : 6.4 |
| 3 | NH ₄ OH | 1 : 11 |
| 4 | 2,2'-Bipyridine | 55 : 45 |
| 5 | 1,10-Phenanthroline | 51.7 : 48.3 |
| 6 | PPh ₃ | 48.6 : 52.4 |
| 7 | dppe | 57.5 : 42.5 |

Reaction conditions: benzonitrile (1 mmol), pFA, [Ru] = [Ru(*p*-cymene)Cl₂]₂, additive, solvent (4 mL in total), 120 °C, 10 h. ^a NMR yield (hexamethyldisilane was used as an internal standard); ratio given at full conversion.

The use of triphenylphosphine increased the yield of benzamide production whereas a slightly higher yield of benzyl alcohol was obtained using dppe. However, as the effects of all these ligands were negligible, and in order to have better atom economy and less waste production as well as to keep the reaction conditions as simple as possible, it was decided that the reactions would be performed in the absence of any additional ligand, because the reaction with dppe (Table 2, entry 7) gave similar results in comparison to the reaction without dppe (Table 1, entry 5).

Following these reactions, the temperature sensitivity and its effect on the product selectivity was investigated. Therefore, the benchmark reaction was done at different temperatures ranging from RT to 130 °C (Table 3, entries 1–6). At low temperatures (Table 3; entries 1–2) the nitrile hydration to benzamide was much faster than the hydrogenation generation, and TH was required for the product formation. Strikingly, a high selectivity was determined for benzyl alcohol (Table 3; entries 3–4) for temperatures as low as 80 °C and 90 °C. Higher temperatures were found to be favorable for the hydration of benzonitrile to benzamide under our conditions such that no benzyl

Table 3 Temperature optimization

| $\text{PhCN} + 10 \text{ eq. pFA} \xrightarrow[\text{H}_2\text{O:toluene (1:1), 25-130}^\circ\text{C, 10 h}]{[\text{Ru}] (1 \text{ mol}\%)} \text{Ph-CH}_2\text{-OH} + \text{Ph-C(=O)-NH}_2$ <div style="display: flex; justify-content: space-around; width: 100%;"> 1 2 </div> | | |
|--|------------|----------------------------|
| Entry | Temp. [°C] | 1 : 2 ^a (ratio) |
| 1 | 25 | 0 : 100 |
| 2 | 60 | <5 : 95 |
| 3 | 80 | 87.5 : 12.5 |
| 4 | 90 | 100 : 0 |
| 5 | 110 | 61.2 : 38.8 |
| 6 | 130 | 0 : 100 |

Reaction conditions: benzonitrile (1 mmol), pFA, [Ru] = [Ru(*p*-cymene)Cl₂]₂, solvent (4 mL in total), 25–130 °C, 10 h. ^a NMR yield (hexamethyldisilane was used as an internal standard); ratio given at full conversion.

Table 4 Loading optimization of pFA

$\text{PhCN} + 1\text{-}9 \text{ eq. pFA} \xrightarrow[\text{H}_2\text{O:toluene (1:1), 90}^\circ\text{C, 10 h}]{[\text{Ru}] (1 \text{ mol}\%)}$
 $\text{Ph-CH}_2\text{-OH} + \text{Ph-C(=O)-NH}_2$

1
2

| Entry | pFA : substrate ratio | 1 : 2 ^a (ratio) |
|-------|-----------------------|----------------------------|
| 1 | 1 : 1 | 0 : 100 |
| 2 | 3 : 1 | 0 : 100 |
| 3 | 5 : 1 | 58.3 : 41.7 |
| 4 | 7 : 1 | 86 : 14 |
| 5 | 8 : 1 | 92 : 8 |
| 6 | 9 : 1 | 100 : 0 |

Reaction conditions: benzonitrile (1 mmol), pFA, [Ru] = [Ru(*p*-cymene)Cl₂]₂, solvent (4 mL in total), 90 °C, 10 h. ^a NMR yield (hexamethyldisilane was used as an internal standard); ratio given at full conversion.

alcohol was detected by increasing temperature up to 130 °C at all (Table 3; entry 6). The highest ratio of benzyl alcohol to benzamide was observed at 90 °C which was selected as the optimum temperature (Table 3; entry 4).

Moreover, the effect of the reduction of the ratio of pFA to the substrate was examined in order to reach the highest possible atom economy in this reaction (Table 4, entries 1–6). As a result, at ratios lower than 5 : 1 of pFA to benzonitrile, no benzyl alcohol can be formed at all. This observation originates from the fact that at lower pFA to benzonitrile ratios, the concentration of dissolved H₂ was not high enough for the deaminative hydrogenation pathway to compete with the hydration of benzonitrile and the formation of benzamide. The very limited solubility of H₂ in water and organic solvents was a crucial parameter to realizing significant H₂ concentrations in solution.^{42–47} Therefore, at least a H₂ saturated solution was needed to overcome the obstacle with catalytic hydration due to the lack of hydrogen. However, when the ratio of 7 : 1 was reached, 86% of benzyl alcohol was produced compared to 14% of benzamide. This ratio was improved further, by employing 8 : 1 and 9 : 1 ratios of pFA to benzonitrile so that the latter resulted in full conversion of the substrate to benzyl alcohol without producing any benzamide. Therefore, a ratio of 9 : 1 of pFA to the substrate was chosen as optimum for the reaction.

The catalyst loading was also evaluated further (Table 5, entries 1–3). The results showed that the reaction can be done even in the presence of lower amounts of Ru(*p*-cymene)Cl₂ dimer although full conversion of the starting material was not achieved within 12 h using 0.2 mol% of it. Furthermore, using 0.5 and 0.2 mol% of the catalyst, the selectivity of benzyl alcohol over benzamide was reduced. The best result was obtained using 1 mol% of the catalyst. Higher catalyst loadings were not tested under these reaction conditions as 1 mol% of the Ru complex already resulted in full conversion of benzonitrile producing benzyl alcohol as the only product of the reaction (Table 5, entry 1). Under these optimized reaction conditions, three control

Table 5 Catalyst loading and control experiments

$\text{PhCN} + 9 \text{ eq. pFA} \xrightarrow[\text{H}_2\text{O:toluene (1:1), 90}^\circ\text{C, 10 h}]{[\text{Ru}] (0\text{-}1 \text{ mol}\%)}$
 $\text{Ph-CH}_2\text{-OH} + \text{Ph-C(=O)-NH}_2$

1
2

| Entry | Cat. (mol%) | 1 : 2 ^a (ratio) |
|-------|--------------------|----------------------------|
| 1 | 1 | 100 : 0 |
| 2 | 0.2 | 54 : 46 ^b |
| 3 | 0.5 | 83.9 : 16.1 |
| 4 | 0.0 (without cat.) | No conversion |
| 5 | 1 (without water) | No conversion |
| 6 | 1 (without pFA) | No conversion |

Reaction conditions: benzonitrile (1 mmol), pFA, [Ru] = [Ru(*p*-cymene)Cl₂]₂, solvent (4 mL in total), 90 °C, 10 h. ^a NMR yield (hexamethyldisilane was used as an internal standard); ratio given at full conversion. ^b After 12 h reaction time.

experiments were performed to make sure that the reaction cannot proceed in the absence of the catalyst, water and pFA (Table 5, entries 4–6). The results confirm the necessity of these reagents for the formation of the alcohol derived from a nitrile. Moreover, ruthenium nanoparticles and other metal precursors were also tested in this reaction, but no activity was observed. Activity was only observed for the dimeric ruthenium arene complexes [Ru(benzene)Cl₂]₂, [Ru(*p*-cymene)I₂]₂ and [Ru(*p*-cymene)Cl₂]₂ (Table S1, ESI†).

It is worth noting that this work has many advantages over the previous reports on this topic. In none of the previous reactions, were imine or amine detected as the by-product of the reaction even if the reaction time was shortened. The reaction was going through the reduction of benzonitrile *via* its corresponding imine which readily converted in equilibrium *via* the hemi-aminal to benzaldehyde, in aqueous media. Thereafter, the latter would be easily, and rapidly, reduced to benzyl alcohol under the reaction conditions. However, as this was the last step, *i.e.*, the reduction of benzaldehyde to benzyl alcohol was happening very fast, and no benzaldehyde can be detected. The other advantage of this reaction was that all of the reactions were not sensitive to air, thus neither precautions such as degassed oxygen-free conditions nor autoclaves for hydrogen gas are required because pFA acts as a hydrogen source in mild conditions. Compared to previous protocols, a higher selectivity can be achieved at a lower temperature with a practical and robust protocol. Furthermore, CO₂ is the only by-product of the degradation of pFA. No ligand, base, or any other special additive is required under these conditions which reduces the amount of waste and increases the atom economy of the reaction. In addition, the catalyst is commercially available and inexpensive.

Substrate scope

The scope of deaminative hydrogenation of a wide variety of aliphatic and aromatic nitriles was investigated using pFA as the hydrogen source. Aliphatic nitriles which are known to be

less active than aromatic ones resulted in their corresponding alcohols successfully without producing any amine or imine as the side product. The conversions were quantitative in most cases during the defined reaction times, and very high yields were obtained. The reaction conditions showed high tolerance for various functional groups (Table 6). In the case of aromatic nitriles, very good to excellent yields were obtained with short reaction times. Aromatic compounds bearing both electron donating and electron withdrawing substituents produced the desired products selectively. Using 4-cyanobenzoic acid as starting material, the nitrile group was converted to its alcohol whereas the carboxylic moiety remained intact (Table 6, entry 5). No coupling product was observed in the reaction of 4-bromo- and 4-iodobenzonitrile under these conditions (Table 6, entries 6, 7). 2-Cyanonaphthalene could also result in the desired primary alcohol with high yield (Table 6, entry 8). However, by increasing the steric hindrance around the cyano group, the rate of the reaction can be reduced such that full conversion of the starting material was not achieved during 16 h (Table 6, entries 9, 10). Phthalide was detected as the major product of the deaminative hydrogenation of phthalonitrile with 66% yield where 26% of the starting material has been converted to 2-cyanobenzyl alcohol (Table 6, entry 11). In this case, after the reductive deamination of one of the nitrile groups resulting in the formation of 2-cyanobenzyl alcohol, the OH group acts as a nucleophile and attacks the neighboring cyano group which after hydrolysis, produces phthalide. Increasing the reaction time in this case will probably cause the rest of the 2-cyanobenzylalcohol (26%) to be converted to phthalide as well. The deaminative hydrogenation of the nitrile group in cinnamonitrile was accompanied with the reduction of the double bond giving 3-phenylpropanol as the product (Table 2, entry 12). Attempts to produce 3-pyridinemethanol from 3-pyridinecarbonitrile, however, were not as successful as expected and isonicotinamide was formed as the main product under the reaction conditions (Table 6, entry 13). This observation is in accordance with the results of Hashmi's work³⁴ where they reported the same trend when employing 3-pyridinecarbonitrile as the starting material. This result can be attributed to the fact that the pyridine ring has a stronger electron withdrawing effect on the cyano group increasing the rate of the competing hydrolysis reaction by facilitating the attack of water molecules to the more electrophilic C^{SP} center and production of nicotinamide. It was also possible that 3-pyridinecarbonitrile was coordinated to the ruthenium as a ligand and poisoned the catalyst.

After screening the aryl nitriles, reactivity of aliphatic nitriles as less reactive substrates were investigated under the optimized conditions. The corresponding primary alcohols could be produced from the aliphatic nitriles not only with good yields but also with higher selectivity compared to the aromatic ones. Aliphatic cyclic nitriles such as benzyl cyanide, cyclohexane carbonitrile and 1-adamantane carbonitrile were converted to the desired products

quantitatively with good yields and selectivity (Table 6, entries 14–17). Linear aliphatic nitriles have also worked as well as the cyclic ones (Table 2, entries 18, 19), however, adiponitrile as a bifunctional nitrile required a longer reaction time to be converted completely to 1,6-hexanediol under the same conditions (Table 6, entry 20).

Production of deuterated alcohols from nitriles

Following these results, this method seems suitable for the production of deuterated alcohols by employing deuterated *para*-formaldehyde (D₂-pFA) in D₂O as D₂ source for the conversion of nitriles to α -deuterated alcohols under similar conditions (Scheme 3). The deuterated product A was formed quantitatively within 24 hours, as confirmed by ¹H-NMR, disappearance of CH₂OH and CH₂OH signals, and the isotope shift of the GC-MS analysis. Within 16 h the degree of deuteration reached 93% for the α,α -dideuterated alcohol and 6.5% of the α -monodeuterated alcohol. By running the reductive deamination with non-deuterated pFA in D₂O, a mixture of α,α -dideuterated alcohol (42.5%), non-deuterated alcohol (32.5%) and α -monodeuterated alcohol was obtained. Therefore, the procedure presented with D₂-pFA and D₂O has the potential to be used for the production of α,α -dideuterated alcohols from nitriles in general.









































Mechanistic studies

Following the previous studies on hydrogen generation from aqueous formaldehyde and pFA,^{27,28} under similar reaction conditions in terms of the pH of the aqueous phase of the system (pH = 5.1), the hydrogen generation in the deaminative reduction followed the same pathway and neither dismutase²⁷ nor the Cannizarro reaction played a role in the degradation of pFA, while the latter one only occurred in strongly basic media (pH > 10). Indeed no methanol was detected and intermediate formed formic acid decomposed solely to CO₂ and H₂ during the formaldehyde reforming.²⁸

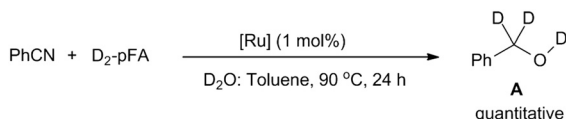
For the identification of the active species the deaminative reduction was conducted with H₂ instead of pFA with the same catalyst precursor. Interestingly, no benzyl alcohol was formed which implied that pFA was required to form the catalytic active species as found in the formaldehyde reforming protocol.²⁸ To underline this assumption the reaction was performed in a two-chamber reaction vessel set-up connected *via* the gas phase (ESI), where one flask contained the catalyst precursor and pFA in a water-toluene mixture for the H₂ production and the second flask contained the catalyst precursor and benzonitrile in a water-toluene mixture. Again, no benzyl alcohol was detected in this type of decoupled TH, instead the benzonitrile was fully converted into benzamide.

Additionally, to obtain further insights the benchmark reaction with benzonitrile as substrate was analysed by ESI-MS to identify complex species carrying different ligands incorporated by ligand exchange during the reaction. Moreover, a complementary reaction was conducted without

Table 6 Substrate scope

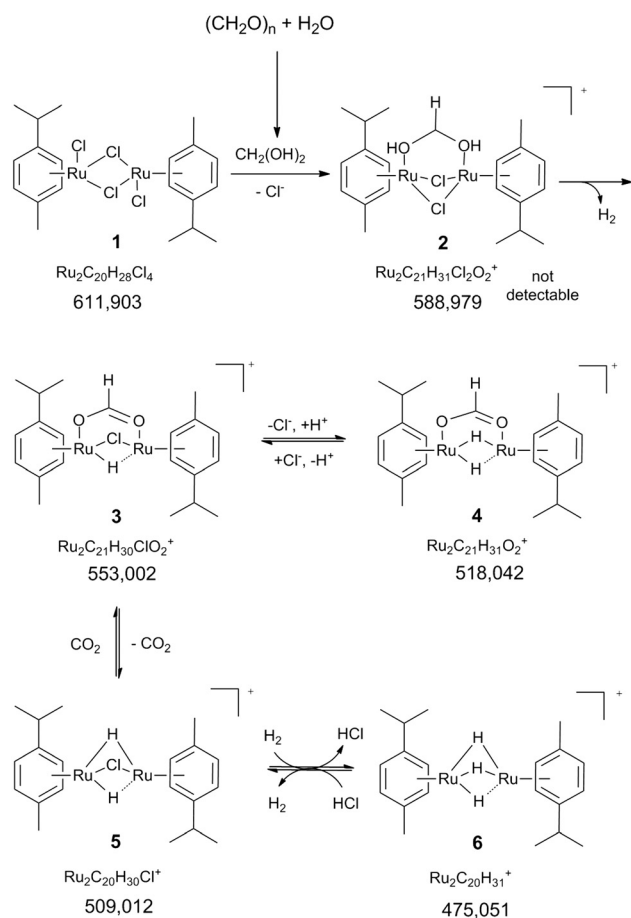
| Entry | Substrate | Reaction | | Product | Yield ^a [%] |
|-----------------|---|-----------------|--|---|------------------------|
| | | RCN + 9 eq. pFA | [Ru] (1 mol%) H ₂ O:toluene (1:1), 90 °C, 10 h | | |
| 1 |  | | |  | 93 |
| 2 |  | | |  | 93 |
| 3 |  | | |  | 92 |
| 4 |  | | |  | 93 |
| 5 |  | | |  | 89 |
| 6 |  | | |  | 88 |
| 7 |  | | |  | 87 |
| 8 |  | | |  | 85 |
| 9 ^a |  | | |  | 83 |
| 10 ^b |  | | |  | 71 |
| 11 ^b |  | | |  | 66 |
| 12 |  | | |  | 89 |
| 13 ^c |  | | |  | 21 |
| 14 |  | | |  | 91 |
| 15 |  | | |  | 87 |
| 16 |  | | |  | 90 |
| 17 |  | | |  | 77 |
| 18 |  | | |  | 88 |
| 19 |  | | |  | 86 |
| 20 ^b |  | | |  | 83 |

Reaction conditions: nitrile (1 mmol), pFA (9 mmol), [Ru] = [Ru(*p*-cymene)Cl₂]₂ (1 mol%), H₂O:toluene (2 mL:2 mL), 90 °C, 16 h. ^a Isolated yield. ^b Reaction time was increased to 24 h. ^c Nicotinamide has been formed as the main product with 74% yield.

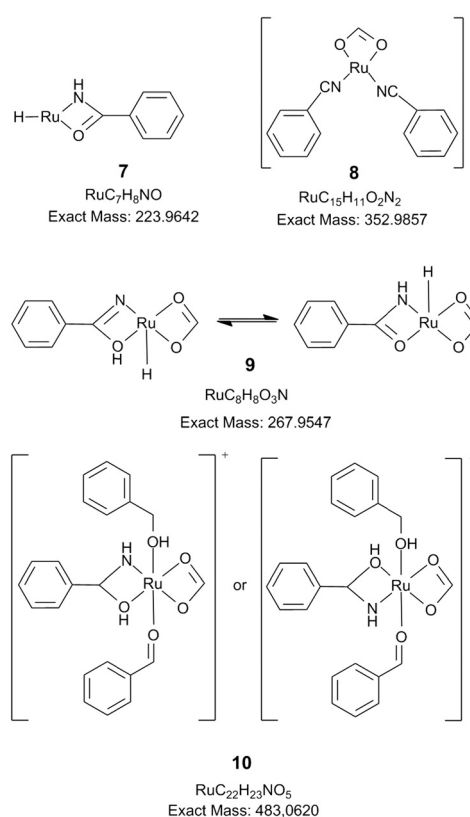


Scheme 3 Production of deuterated primary alcohols using D_2 -pFA in D_2O : toluene.

pFA. An aliquot was taken after 4 h from each reaction. The ESI-MS data of the deaminative reduction showed that the decomposition of pFA *via* aqueous formaldehyde to H_2 and CO_2 in the presence of $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ **1** resulted in the formation of the dimeric species $[(\text{Ru}(p\text{-cymene}))_2\mu\text{-H}(\mu\text{-HCO}_2)_2\mu\text{-Cl}]^+$ **3** (m/z : 553.002 amu) as previously reported,²⁸ whereas the short-living methanediol complex **2** cannot be detected. This indicated that the pFA decomposition also occurs in the presence of nitrile in toluene. In addition, $[(\text{Ru}(p\text{-cymene}))_2(\mu\text{-H})_2(\mu\text{-HCO}_2)]^+$ **4** (m/z : 518.042 amu) was detected, which was formed by ligand exchange. Also, $[(\text{Ru}(p\text{-cymene}))_2(\mu\text{-H})_2\mu\text{-Cl}]^+$ **5** (m/z : 509.012 amu) which was formed upon decarboxylation of the formiato ligand and $[(\text{Ru}(p\text{-cymene}))_2(\mu\text{-H})_3]^+$ **6** (m/z : 475.051 amu) which was formed *via* heterolytic cleavage of H_2 and the substitution of the halide



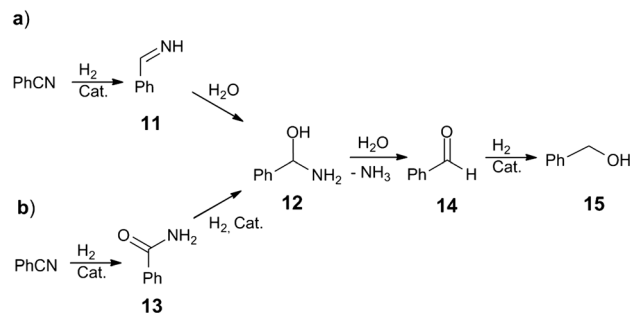
Scheme 4 The formation of dimeric complexes during pFA degradation in the reductive deamination of nitrile.



Scheme 5 The structures of some of the unsaturated species **7–9** and the intermediate/product complex **10** detected by ESI-MS from aliquots of the reaction mixture.

ligand (Scheme 4). The ESI MS spectra did not even show traces of $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ which means that it had been converted completely to the other more reactive species under these conditions. These observations were in agreement with the results of previous work on the degradation of (*para*)formaldehyde in the presence of the same catalyst but in the absence of nitrile.^{26–28}

After confirming the pFA degradation pathway under these conditions, the ESI-MS data was analysed further to get insights into the reductive deamination of benzonitrile. Different pathways were possible for such transformation

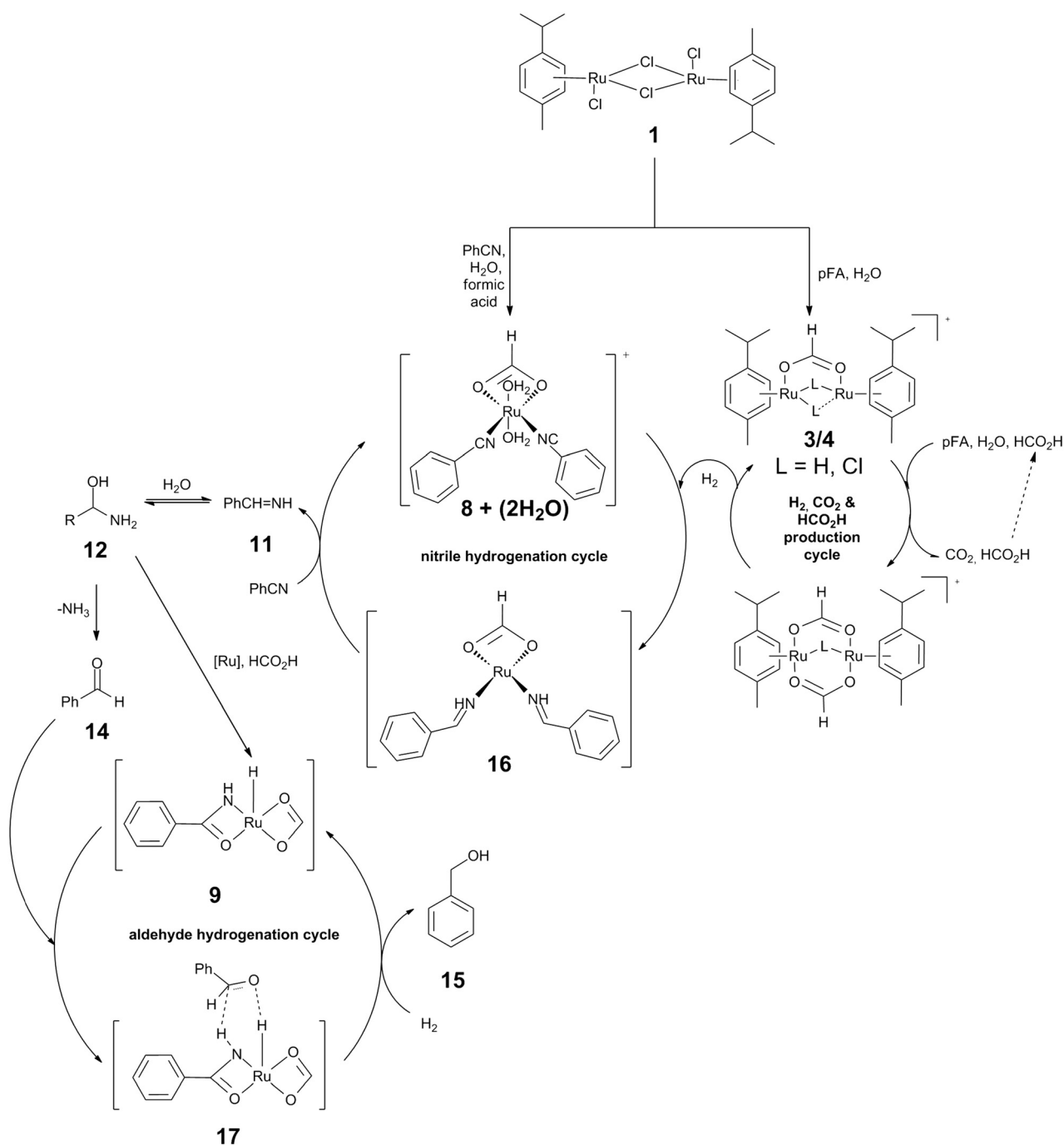


Scheme 6 Two possible pathways (a and b) for the formation of the hemi-aminal intermediate **12** as a potential intermediate for the formation of benzyl alcohol.

which can be divided into two categories: (I) the one with the dimeric catalytic species, and, (II) the one involving the monomeric ruthenium species. The data showed that no dimeric ruthenium species containing different combinations of the catalyst and benzonitrile and pFA in the spectrum can be detected. Likewise, no complex species carrying ligands such as benzamide or benzaldehyde were formed from benzonitrile. In addition, under these conditions no ligand exchange between *p*-cymene and toluene could be observed for the dimeric ruthenium species. Taking the previously

reported observations into account, the direct involvement of the dimeric complexes 2–6 for the deaminative reduction of nitriles was excluded. Therefore, the reaction mechanism most likely involved monomeric ruthenium species. The comparison of the ESI MS spectra of the benchmark reaction with the pFA-free blank reaction, enabled easier identification of the ruthenium species carrying benzonitrile as ligand.

As has been mentioned previously, benzonitrile, *per se*, can coordinate to the ruthenium center *via* its nitrogen lone pair or its triple bond. In 2010, Sabo-Etienne investigated the



Scheme 7 The proposed reaction pathway for the deaminative reduction of nitriles.

mechanism of the hydrogenation of benzonitrile in the presence of $\text{RuH}_2(\sigma\text{-H}_2)_2(\text{PCyp}_3)_2$ as catalyst to produce amine. This showed that under their conditions, benzonitrile can be coordinated to the ruthenium center *via ortho*-directed C–H activation. The formation of such an intermediate enabled the imine intermediate to be trapped and be reduced to amine before it was hydrolysed to benzaldehyde. Therefore, considering that in this case benzyl alcohol is the only product, such species were not expected. This assumption was verified by the absence of any possible species of this kind in the ESI-MS spectra. It is also worth noting that none of the expected primary, secondary and tertiary amines resulting from the simple reduction of benzonitrile³¹ existed in the reaction mixture according to the spectra. Interestingly, signals were found in the ESI-MS which could be assigned to the exact masses of the monomeric ruthenium species 7–9 (Scheme 5) carrying benzonitrile or benzamide (derived from the corresponding hemi-aminal), whereas the absence of all the potential related dimeric species in the spectra, confirmed the assumption of the involvement of the monomeric ruthenium intermediate in the course of the deaminative reduction (Scheme 6). The exact formation of these species 7–9 was unknown, although a cascade of ligand exchange reactions in the presence of an excess of nitrile is most likely to be an important issue. However, highly-unsaturated species were usually formed under MS-conditions due to the loss of ligands during the measurement,²⁸ therefore in solution the vacant coordination sites were occupied by neutral molecules from the reaction mixture (*e.g.*, H_2O , substrates, intermediates and products). Strikingly, a ruthenium species 10 (Scheme 5) was also detected carrying three intermediates as ligands: hemi-aminal, benzaldehyde and benzyl alcohol which gave further indications that these monomeric species were involved in the nitrile hydrogenation.

This lead us two possible reaction pathways (Scheme 6a and b). In the first one, benzonitrile could be reduced to the imine intermediate 11 under the reaction conditions which would be converted to the hemi-aminal 12 immediately due to the presence of plenty of water molecules in the medium.³⁴ In the other pathway, benzonitrile could be hydrolysed initially to benzamide 13 which could then be subsequently reduced to 12 in the presence of the catalyst and the hydrogen formed *in situ*.⁴⁸ Releasing NH_3 from 12 formed benzaldehyde 14 in both pathways which then, could be easily reduced to benzyl alcohol 15 under the reaction conditions.

To distinguish between the pathways in Scheme 6, an experiment was performed using benzamide as substrate instead of benzonitrile. If benzyl alcohol can be produced from benzamide as well, it could be concluded that the second pathway in Scheme 6 was valid in this case. However, no benzyl alcohol was detected after 24 h under these conditions and only starting material could be observed in the NMR spectrum. Therefore, this pathway can be excluded.

Based on these evidence and the previous studies in the field,^{34,48–51} the following reaction pathway can be proposed

for the reductive deamination of nitriles using pFA in aqueous media (Scheme 7). Initially, $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ 1 reacted in two different pathways: (I) the dimeric complexes 3 and 4 were formed by reforming pFA in water,²⁸ which then produced (catalytically) H_2 , CO_2 and formic acid over the course of the reaction (Scheme 7: hydrogen production cycle). (II) Complex 1 was converted into complex 8 which readily reacted with the hydrogen produced *in situ*, then yielded the benzylimine 11 (Scheme 7: nitrile hydrogenation cycle) which was converted to benzaldehyde 14 *via* the hemi-aminal 12 in equilibrium followed by NH_3 extrusion because of the large excess of water. The hemi-aminal 12 could also react with one of the ruthenium species present in the medium to form species 9. Benzaldehyde 14 could then react with complex 8 in a Noyori-type HT reaction *via* the transition state 17 and then yielding benzyl alcohol and the catalytically active species 9 was regenerated (Scheme 7: aldehyde reduction cycle). In particular the intermediates 8–10 (Scheme 5) support the proposed catalytic nitrile hydrogenation and deamination as depicted in Scheme 7.

Conclusions

In summary, the reductive deamination of different kinds of aliphatic and aromatic nitriles was reported for the first time using *para*-formaldehyde as a hydrogen donor under mild and practical reaction conditions because no air or moisture sensitive chemicals or special glassware are required. The reaction has a high selectivity for the production of primary alcohols in the presence of the ruthenium dichloro(*p*-cymene)ruthenium(II) dimer used as an air-stable and commercially available catalyst and does not result in the formation of any amine or other possible side products with this protocol. The analysis of the ESI-MS data also revealed the nature of the catalytically active species in this transformation. Based on these results, the reaction mechanism contains three different catalytic cycles: (I) a hydrogen generation cycle, (II) a nitrile hydrogenation cycle, and, (III) an aldehyde hydrogenation cycle. In the degradation of pFA to CO_2 and H_2 , the dimeric ruthenium complexes are involved, while the involvement of benzonitrile in the following catalytic cycles results in the formation of *N,O*-coordinated monomeric species, which act as the active catalyst in the reductive deamination of nitriles in the following cycles. It is worth noting that the ruthenium nanoparticles showed no activity under these reaction conditions.

Based on these data, as well as other experimental observations, a plausible mechanism was also proposed for this reaction, although more mechanistic studies are required to reveal further aspects about the reaction pathway. The authors believe that this work can open-up a new avenue in the field of transfer hydrogenation.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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