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Ruthenium-Catalyzed Deaminative Hydrogenation of Aliphatic and Aromatic Nitriles to Primary Alcohols

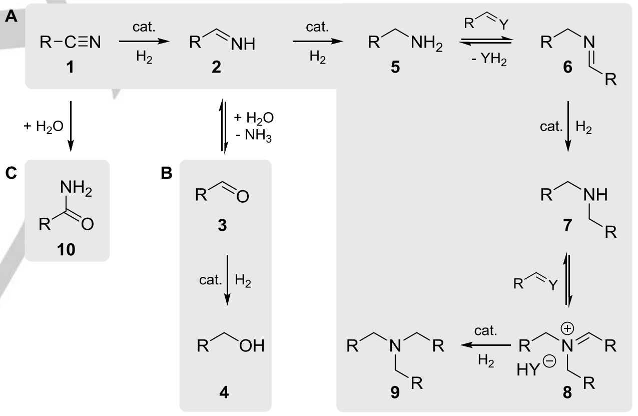
István Gábor Molnár,[a] Pilar Calleja,[a] Martin Ernst,[b] A. Stephen K. Hashmi,[a,c] and Thomas Schaub*[a,b]

This work is dedicated to David Milstein in honor of his 70th birthday.

Abstract: The deaminative hydrogenation of nitriles towards alcohols is a useful reaction to transform nitriles into alcohols with NH_3 as the sole by-product. Using the simple and robust $RuHCl(CO)(PPh_3)_3$ as the catalyst, at low H_2 pressures a series of aliphatic and aromatic nitriles can be transformed into the corresponding alcohols. Suitable solvent systems for these reactions are 1,4-dioxane/water or EtOH/water mixtures. In most cases the selectivity for the alcohols is excellent and the corresponding amines are formed only in trace amounts.

The conversion of the nitrile group *via* hydrolytic or reductive transformations has become a versatile and broadly used synthetic tool for the installation of a large variety of functional groups, ranging from carboxylic acids to amines.[1] Therefore, considerable research efforts have been focusing on the development of efficient catalytic protocols that allows for the selective transformation of nitriles into valuable end-products, while avoiding the generation of stoichiometric amounts of waste. In particular, the catalytic hydrogenation of nitriles to form primary or secondary amines has drawn considerable attention, demonstrated by numerous reports appeared in the recent literature.[2-4] In contrast, research on the direct catalytic conversion of nitriles into primary alcohols is lagging behind significantly with only a handful of reports on this subject existing.[5,6] Some of the disadvantages of the current protocols are: 1) the low selectivity towards the formation of the alcohol, especially with heterogeneous catalysts, 2) the narrow substrate scope, and 3) the need for the use of either high hydrogen pressures (30-70 bar) or high temperatures (up to 300 °C). Therefore, our aim was to develop an operationally simple and general protocol for the direct catalytic conversion of nitriles into primary alcohols under relatively mild conditions.

Mechanistically, the catalytic reduction of the nitrile group with molecular hydrogen proceeds through a number of equilibria, having imine **2** as key intermediate (Scheme 1, **A**).[4a, 7] Hence, the formation of primary amine **5** is often accompanied by the formation of secondary (**7**) and sometimes tertiary amines (**9**). Building on this mechanism, we envisioned a process in which intermediate **2** could be directly hydrolyzed to aldehyde **3** that through a consecutive hydrogenation step can be converted further to form the corresponding primary alcohol (**4**) which was the focus of this study (Scheme 1, **B**). As a possible side reaction, the direct hydrolysis of the nitrile group to amide **10** was also identified (Scheme 1, **C**), although in the absence of strong acids and bases[8] or certain transition metal complexes,[9] the rate of this competing process was expected to be negligible.



Scheme 1. A) Hydrogenation of nitriles under anhydrous conditions to form primary, secondary, and tertiary amines. B) Proposed path towards primary alcohols under aqueous conditions. C) The formation of amides as possible side products.

As Ru-pincer complexes were reported by Milstein *et al*. to be excellent precatalysts in deamination reactions,[10] we started our investigation with the evaluation of complexes **A**, **B** and **C** for the deaminative hydrogenation of *n*-octanenitrile (**1a**) selected as model substrate. Under the initial reaction conditions (140 °C, 10 bar H_2, and a 1:1 mixture of 1,4-dioxane and water as solvent) acridine-based complexes **A**[11] and **B**[12] showed excellent activity, albeit their selectivity towards the desired alcohol (**4a**) was relatively low and thus a significant amount of *n*-octylamine (**5a**) was also obtained (Table 1, entries 1 and 2). Ru(II)-triphos complex **C,**[13] featuring 1,1,1-tris(diphenylphosphinomethyl) ethane as tridentate ligand, was proved to be a less effective catalyst due to the slightly lower yield and selectivity observed. (entry 3). In this case tri-*n*-octylamine (**9a**) was identified as the

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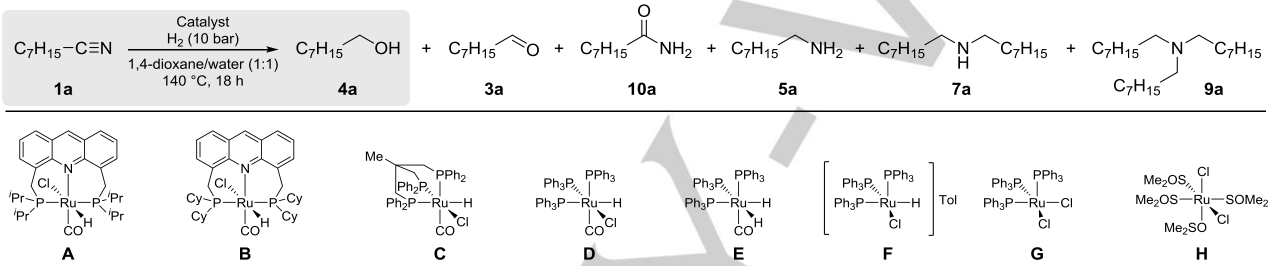
major side product without the detection of primary amine **5a** obtained previously with complexes **A** and **B** (entry 3 *cf.* entries 1 and 2). Based on these initial results, we turned our attention towards Ru(II)-complexes featuring monodentate ligands (**D**-**F**). Gratifyingly, RuHCl(CO)(PPh$_3$)$_3$(**D**)[14] provided us with the desired product (**4a**) with remarkable selectivity, although this Ru(II)-complex was found to be significantly less active than the pincer-complexes tested (entry 4 cf. entries 1-3). When the catalyst loading was increased from 0.5 mol% to 1.0 mol% the conversion could be driven to near completion without the loss of selectivity (entry 5). Furthermore, whilst shortening the reaction time gave lower overall conversion, none of the possible intermediates (**2** or **3**) were detected in any significant quantity (see in SI, entry 6). With this in mind, we wanted to gain insight into the role of the Cl$^-$ and CO ligands on the Ru(II)-complex. Whereas replacing the chloride with a hydride (**D**→**E**) in the precatalyst showed no significant effect on the performance, the loss of the stabilizing CO ligand and PPh$_3$ (**D**→**F, G, H** and **RuCl$_3$**) affected detrimentally the selectivity of the transformation (entries 9, 10, 12) or both the activity and selectivity (entries 7 and 11). In these cases, the main products were the dialkyl- and/or trialkylamine. To rule out the possibility that small amounts of heterogeneous Ru would be responsible for the catalytic activity, Ru/C (5% *w*/*w*) was also tested as a catalyst. As shown in entry 8, a significant drop in the selectivity was observed with this catalyst and only traces of the desired alcohol (**4a**) could be detected, whilst the reaction went to completion (entry 8). Finally, a control experiment showed that the transformation does not proceed without the addition of any catalyst, revealing only unreacted starting material by GC analysis (see in SI, entry 14).

Table 1. Catalytic deaminative hydrogenation of *n*-octanenitrile (**1a**) to *n*-octanol (**4a**).

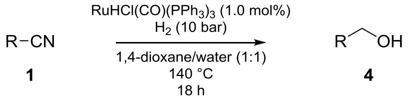


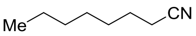
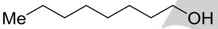
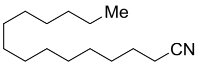
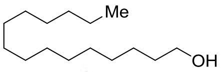
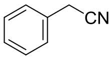
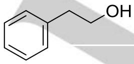
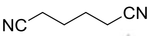
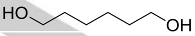
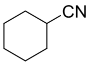
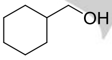
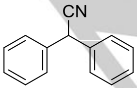
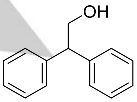
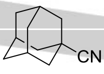
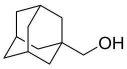
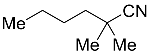
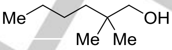
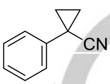
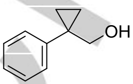
Entry	Catalyst	Solvent	Conc. [mol/L]	Temp. [°C]	Conv. [%][b]	GC yield [%][b]					
						4a	3a	10a	5a	7a	9a
1	A (0.5 mol%)	1,4-dioxane/water (1:1)	0.167	140	>99	79	<1	<1	16	2	<1
2	B (0.5 mol%)	1,4-dioxane/water (1:1)	0.167	140	>99	79	<1	<1	17	2	<1
3	C (0.5 mol%)	1,4-dioxane/water (1:1)	0.167	140	>99	73	<1	1	<1	3	23
4	D (0.5 mol%)	1,4-dioxane/water (1:1)	0.167	140	88	79	<1	1	<1	1	<1
5	D (1.0 mol%)	1,4-dioxane/water (1:1)	0.167	140	97	92	<1	<1	<1	1	<1
6	E (0.5 mol%)	1,4-dioxane/water (1:1)	0.167	140	87	77	<1	1	<1	<1	<1
7[c]	F (0.5 mol%)	1,4-dioxane/water (1:1)	0.167	140	51	8	<1	3	8	23	3
8	5 *w*/*w*% Ru/C (0.5 mol%)	1,4-dioxane/water (1:1)	0.167	140	>99	7	<1	<1	12	50	26
9	RuCl$_3$ (0.5 mol%)	1,4-dioxane/water (1:1)	0.167	140	>99	<1	<1	<1	6	24	42
10	RuCl$_3$ (0.5 mol%) + PPh$_3$ (1.5 mol%)	1,4-dioxane/water (1:1)	0.167	140	>99	4	<1	<1	<1	29	29
11	G (0.5 mol%)	1,4-dioxane/water (1:1)	0.167	140	61	9	<1	4	<1	20	6
12	H (0.5 mol%)	1,4-dioxane/water (1:1)	0.167	140	>99	11	<1	5	<1	27	34
13	D (1.0 mol%)	EtOH/water (1:1)	0.167	140	94	87	<1	1	<1	1	<1
14	D (1.0 mol%)	toluene/water (1:1)	0.167	140	56	13	<1	5	8	29	<1
15	D (1.0 mol%)	water	0.167	140	>99	50	<1	16	<1	19	6
16	D (1.0 mol%)	1,4-dioxane/water (1:1)	0.5	140	>99	94	<1	1	<1	1	1
17[d]	D (1.0 mol%)	1,4-dioxane/water (1:1)	0.5	140	>99	95	<1	1	<1	1	<1

[a] Reaction conditions: *n*-octanenitrile (3.0 mmol), catalyst (0.5 mmol%), 1,4-dioxane (9.0 mL) and water (9.0 mL) were heated in a glass autoclave at 140 °C under 10 bar H_2 pressure for 18 h. [b] Determined by GC analysis using anisole as internal standard. [c] Formation of Ru black. [d] Reagents were handled under air and the reaction mixture flushed with nitrogen (3-5X) and hydrogen (3-5X) prior to pressurization with hydrogen.

Solvent, temperature, and concentration effects were evaluated in order to optimize the reaction conditions. It was observed that not only 1,4-dioxane/water but also EtOH/water mixtures were suitable solvent systems for the deaminative hydrogenation of nitrile **1a**, providing both high conversion and yield (Table 1, entry 5 *cf*. entry 13). In contrast, the biphasic toluene/water mixture proved to be an inefficient solvent system, as the reaction became sluggish with a significant drop in the selectivity (entry 14). The presence of an organic solvent, however, was found to be essential for achieving high levels of selectivity, as water alone provided only inferior results (entry 15). Decreasing the temperature gave lower conversion to the corresponding alcohol, but had no effect on the selectivity (see in SI, entries 20 and 21). The application of higher substrate concentrations proved to be beneficial as the conversion could be driven to completion, without the loss of the selectivity (entry 16). It was also demonstrated that the reaction is not sensitive to small amounts of oxygen; thus all reagents could be handled under air and flushing the system with nitrogen prior to pressurization with hydrogen was sufficient (entry 17).

Table 2. Catalytic deaminative hydrogenation of aliphatic nitriles.[a]

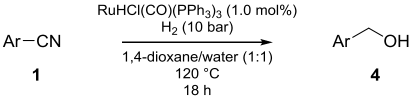


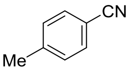
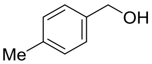
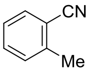
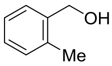
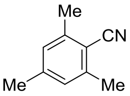
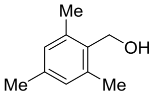
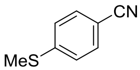
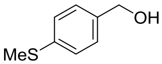
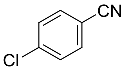
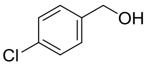
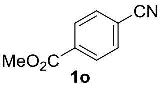
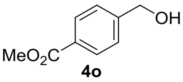
Entry	Nitrile **1**	Alcohol **4**	Yield [%]
1	 **1a**	 **4a**	95
2	 **1b**	 **4b**	90
3	 **1c**	 **4c**	89
4[b]	 **1d**	 **4d**	88
5	 **1e**	 **4e**	93
6	 **1f**	 **4f**	92
7	 **1g**	 **4g**	97
8	 **1h**	 **4h**	91
9	 **1i**	 **4i**	95

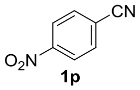
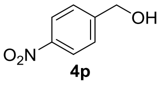
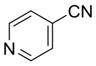
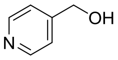
[a] Reaction conditions: nitrile (3.0 mmol), RuHCl(CO)(PPh_3)$_3$ (1.0 mmol%), 1,4-dioxane, and water were heated in a glass autoclave at 140 °C under 10 bar H_2 pressure for 18 h. [b] Reaction was run for 42 h.

With the optimized reaction conditions in hand, we turned our attention to the substrate scope of our deaminative hydrogenation protocol. The results are summarized in Tables 2 and 3. Aliphatic nitriles, which were previously shown to be problematic substrates,[5a] all cases showed full conversion and provided good to excellent yields (Table 2, entries 1-3). Furthermore, adiponitrile (**1d**), which contains two nitrile groups, could be converted to the corresponding diol **4d** in good yield, although the reaction time had to be extended to achieve full conversion (entry 4). Compounds with a nitrile group on a tertiary or quaternary carbon atom were also excellent substrates for the transformation, affording the desired products in very good yields (entries 5-9).

Table 3. Catalytic deaminative hydrogenation of aromatic nitriles.[a]



Entry	Nitrile **1**	Alcohol **4**	Yield [%]
1	 **1j**	 **4j**	92
2	 **1k**	 **4k**	95
3[b]	 **1l**	 **4l**	9[c]
4	 **1m**	 **4m**	89
5	 **1n**	 **4n**	87
6	 **1o**	 **4o**	49

7[d]	 **1p**	 **4p**	22 [e,f,g]
8	 **1q**	 **4q**	48[h]

[a] Reaction conditions: nitrile (3.0 mmol), $RuHCl(CO)(PPh_3)_3$ (1.0 mmol%), 1,4-dioxane, and water were heated in a glass autoclave at 120 °C under 10 bar H_2 pressure for 18 h. [b] Reaction was carried out at 140 °C and run for 69 h. [c] Starting material was recovered in 88%. [d] Reaction was carried out at 140 °C. [e] Formation of Ru black. [f] Starting material was recovered in 7%. [g] 4-Aminobenzonitrile and 4-nitrobenzamide (**10p**) were isolated as major side products in 14 and 41% yields, respectively. [h] Isonicotinamide **10q** was isolated as major side product in 47% yield.

Our deaminative hydrogenation methodology was successfully applied to aromatic nitriles (**1j-1q**) as well (Table 3). In this case, considerable amounts of the corresponding amides (**10**) were detected in the crude mixtures suggesting that the rate of the competing hydrolysis is faster. To suppress this undesired side reaction, the reaction temperature was decreased to 120 °C. Under these modified reaction conditions benzonitriles featuring a methyl group either in the para (**1j**) or in the ortho position (**1k**) were converted to the corresponding benzyl alcohols **4j** and **4k** in high yields (Table 3, entries 1 and 2). In contrast, substrate **1l** with two ortho substituents was more problematic and provided only low conversion and yield even under more forcing conditions (entry 3).[15] While *p*-thiomethyl (**1m**) and *p*-chloro (**1n**) substituents were well tolerated by the reaction, the presence of strongly electron withdrawing groups, such as the methoxycarbonyl group (**1o**) or the nitro (**1p**), proved to be disadvantageous for achieving high levels of yield and selectivity (entries 4 and 5 *cf.* entries 6 and 7). Compound **1q** featuring a heteroaromatic ring could also be converted to the desired alcohol **4q**, albeit with moderate yield due to the formation of isonicotinamide (**10q**) as side product (entry 8).

In conclusion, we developed an operationally simple and highly selective transformation for the direct conversion nitriles to primary alcohols, using the commercially available and inexpensive $RuHCl(CO)(PPh_3)_3$ as catalyst. As the reaction requires the use of relatively low pressures of hydrogen, it can be conducted in Fischer-Porter-type glass autoclaves that are easier to handle and more cost-efficient than high pressure steel autoclaves. Moreover, our methodology was found to be suitable for the conversion of not only aromatic but also aliphatic nitriles and also features a relatively broad functional group tolerance.

Experimental Section

General procedure for Tables 2 and 3:

A ca. 80 mL Fischer-Porter-type glass autoclave was charged with $RuHCl(CO)(PPh_3)_3$ (0.03 mmol, 28.6 mg), the specified nitrile (3.0 mmol), degassed 1,4-dioxane (3.0 mL) and degassed water (3.0 mL) under air. After closing the reaction vessel, the system was purged first with nitrogen (3-5×) and then with hydrogen (3-5×). Finally, the autoclave was pressurized with hydrogen (10 bar) and placed into a preheated oil bath (120 or 140 °C). The reaction mixture was then stirred at the specified temperature for 18 h, before the heating bath was removed and the system was cooled to room temperature. After depressurization, the crude mixture was diluted with brine (ca. 10 mL) and the resulting biphasic mixture was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude material obtained was then purified by flash column chromatography on silica gel providing the desired primary alcohol.

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Keywords: Nitriles • Deamination • Hydrogenation • Alcohols • Ruthenium

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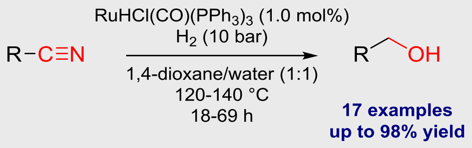
COMMUNICATION



- Inexpensive and robust catalyst
- Relatively mild conditions
- Operationally simple procedure
- High selectivities and yields
- Aliphatic and aromatic nitriles

complex was found to be a highly efficient and selective catalyst for the direct deaminative hydrogenation of nitriles to form primary alcohols. The reaction proceeds under relatively mild conditions and gives generally high yields for both aliphatic and aromatic nitriles.

*Dr. István Gábor Molnár, Dr. Pilar Calleja, Dr. Martin Ernst, Prof. Dr. A. Stephen K. Hashmi, and Dr. Thomas Schaub**

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Ruthenium-Catalyzed Deaminative Hydrogenation of Aliphatic and Aromatic Nitriles to Primary Alcohols