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A Mild and Base-Free Protocol for the Ruthenium-Catalyzed Hydrogenation of Aliphatic and Aromatic Nitriles with Tridentate Phosphine Ligands

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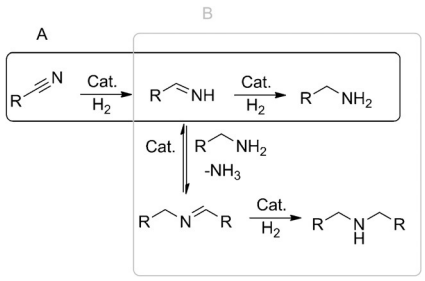
A novel protocol for the general hydrogenation of nitriles in the absence of basic additives is described. The system is based on the combination of [Ru(cod)(methylallyl)$_2$] (cod = cyclooctadiene) and **L2**. A variety of aromatic and aliphatic nitriles is hydrogenated under mild conditions (50 °C and 15 bar H_2) with this system. Kinetic studies revealed higher activity in the case of aromatic nitriles compared with aliphatic ones.

Introduction

Amines are present in natural compounds such as nucleotides, neurotransmitters, and amino acids, which play an important role in biological processes. Moreover, a large number of industrially relevant dyes, solvents, additives, anti-foam agents, detergents, agrochemicals, and drugs contain amines in their structure.[1] In particular, primary amines are of interest as they are essential intermediates that can easily be modified by follow-up reactions to obtain secondary and tertiary amines,[2] for example, through reductive amination[3] or N-alkylation with alcohols[4] or carboxylic acids.[5] Among the available methodologies for the synthesis of primary amines,[6] nitrile reduction constitutes a clean and atom economical approach.[7] On a laboratory scale, nitriles are commonly reduced with stoichiometric amounts of metal hydrides such as $LiAlH_4$ or $NaBH_4$, generating metal salts as waste.[8] Thus, hydrogenation of nitriles constitutes a more environmentally benign and clean methodology to obtain primary amines. In industry, heterogeneous catalysts, usually Raney®-Ni and -Co, are the selected ones for performing such reactions.[9] However, these catalysts do not tolerate some functional groups and/or need additives, such as ammonia, to avoid the formation of side products.

After pioneering work in the 1980s[10] based in the use of Ru or Rh hydride complexes, recently several catalyst systems for nitriles hydrogenation based on Ru,[11] Ir,[12] Re,[13] and Mo[14] have been described. Remarkably, also non-noble metal systems have been successfully applied to this reaction. For example, two Fe pincer complexes[15] developed by our group and Milstein's group and a Co pincer complex[16] published by Milstein and co-workers are the most representative examples.

Despite all these advances, nitrile hydrogenation is still an interesting reaction in terms of selectivity. As shown in Scheme 1, initially the nitrile is hydrogenated to the primary imine, which leads either the desired primary amine (pathway A), or to the secondary amine or imine (pathway B). To avoid the formation of the latter products, derived from pathway B, several strategies can be applied, the addition of a base to shift the equilibrium to the primary imine being the most frequent. Furthermore, it has been showed that in some cases a basic additive not only has a positive effect on the selectivity, but also on the performance of the catalyst.[11g] Hence, the development of more active catalytic systems that can perform nitrile hydrogenation selectively without the need for any additive is highly desirable. Currently, only a few Ru systems[11a,b,d,e] as well as a Fe–PNP complex[15a] are known to perform nitrile hydrogenation in the absence of base.



Scheme 1. Catalytic hydrogenation of nitriles to primary amines (A) and possible side reaction (B).

Recently, our group has reported the synthesis of novel tridentate phosphine ligands that are inspired by the so-called triphos ligand (Figure 1).[17]

Catalytic applications of these systems included the production of γ-valerolactone from biomass derivatives, such as methyl levulinate and levulinic acid.[18] Based on our previous experience in nitrile hydrogenation using the combination of [Ru(cod)(methylallyl)$_2$] (cod = cyclooctadiene) and monodentate or bidentate P- or PN- ligands in the presence of a basic additive, we decided to explore this reaction using the new tridentate ligands.

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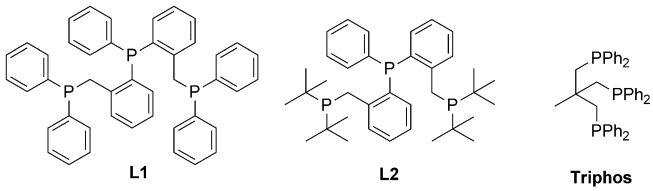
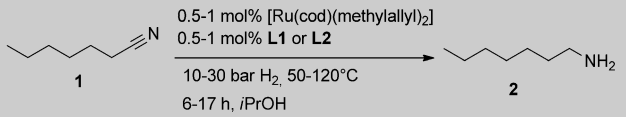


Figure 1. Tridentate phosphine-type ligands.

Results and Discussion

1-Heptanenitrile **1**, a more demanding substrate in comparison with aromatic ones, was selected as the model compound to initiate this study (Table 1). First, tridentate ligands **L1** and **L2** were tested for the hydrogenation of 1-heptanenitrile **1** in the presence of [Ru(cod)(methylallyl)$_2$] 1 mol% and KO*t*Bu 10 mol% at 120 °C and 30 bar of H_2 for 17 h (Table 1, entries 1 and 2). Under these conditions, heptyl amine **2** was obtained in quantitative yield in the case of **L2**, whereas for **L1** only 56% of the amine was detected. At lower temperature (70 °C), [Ru(cod)(methylallyl)$_2$]/**L2** system was equally active, giving heptyl amine **2** in excellent yields (Table 1, entry 4). In contrast, in the presence of **L1**, heptyl amine **2** was formed in low yields (6%, Table 1, entry 3), confirming the lower efficiency of this catalytic system. Further investigation of reaction time, temperature, and pressure with [Ru(cod)(methylallyl)$_2$]/**L2** (Table 1, entries 5–7) showed that it was possible to obtain heptyl amine **2** in excellent yields at 50 °C and 15 bar of H_2 in 6 h by using 1 mol% of the catalyst. Moreover, the catalyst performance did not decrease when using 0.5 mol% of the Ru/**L2** system at a longer reaction time of 17 h (Table 1, entry 9). To our delight, the hydrogenation of 1-heptanenitrile **1** afforded heptyl amine **2** in quantitative yields when the [Ru(cod)(methylallyl)$_2$]/**L2** combination was used in the absence of any basic additive (Table 1, entry 10).

Table 1. Hydrogenation of 1-heptanenitrile 1 with [Ru(cod)(methylallyl)$_2$] and **L1** or **L2**: optimization of reaction conditions.[a]



Entry	Cat. [mol%]	Ligand	Additive	*T* [°C]	Conv. [%][b]	Yield **2** [%][b]
1[c]	1	**L1**	KO*t*Bu	120	100	56
2[c]	1	**L2**	KO*t*Bu	120	100	>99
3[c]	1	**L1**	KO*t*Bu	70	18	6
4[c]	1	**L2**	KO*t*Bu	70	100	>99
5[c,d]	1	**L2**	KO*t*Bu	70	100	>99
6[c,d]	1	**L2**	KO*t*Bu	50	94	94
7[d]	1	**L2**	KO*t*Bu	50	96	95
8[d]	0.5	**L2**	KO*t*Bu	50	84	82
9	0.5	**L2**	KO*t*Bu	50	99	98
10	**0.5**	**L2**	–	**50**	**100**	**>99**
11[e]	0.5	**L2**	–	50	96	95
12	0.5	**L2**	–	RT	–	–
13[f]	0.5	**L2**	–	50	–	–
14[g]	0.5	**L2**	–	50	20	–
15	0.5	–	–	50	–	–

[a] Standard reaction conditions: 1-heptanenitrile (0.5 mmol, 55.6 mg), [Ru(cod)(methylallyl)$_2$] (0.5–1 mol%), **L1** or **L2** (0.5–1 mol%), KO*t*Bu (10 mol%), dry *i*PrOH (2 mL), 15 bar H_2, 17 h. [b] Conversion of **1** and yield of **2** were calculated by GC by using hexadecane as an external standard. [c] 30 bar H_2. [d] The reaction time was 6 h. [e] 10 bar H_2. [f] No H_2 pressure. [g] First, [Ru(cod)(methylallyl)$_2$]/**L2** (0.5 mol%) in dry *i*PrOH (2 mL) was preactivated with 15 bar H_2, at 50 °C, for 1 h, then, 1-heptanenitrile (0.5 mmol) was added and the reaction was run at 50 °C, 17 h, with no H_2 pressure; 18% of *N*-benzylpropan-2-imine was formed.

At this point, the influence of different solvents in the hydrogenation of 1-heptanenitrile **1** under the optimized reaction conditions (Table 1, entry 10) was assessed (Figure 2). Interestingly, the primary amine was obtained in excellent yield only in *i*PrOH. Primary alcohols MeOH and EtOH gave also total conversion of the 1-heptanenitrile, although with no selectivity to the primary amine. MeOH afforded the secondary imine as the only product, while EtOH gave a mixture of the secondary imine and amine. Other solvents, such as toluene, THF, and dioxane, did not afford any conversion of 1-heptanenitrile **1**. The fact that the reaction only works in alcohol-type solvents encouraged us to explore the possibility of a hydrogen transfer mechanism. With that aim, the hydrogenation of 1-heptanenitrile was run in the absence of hydrogen, with and without preactivation of the [Ru(cod)(methylallyl)$_2$]/**L2** system with hydrogen (Table 1, entries 13 and 14). Only in the experiment with hydrogen pretreatment was some conversion detected (20%), identifying *N*-benzylpropan-2-imine as the only product. In addition, the hydrogenation of benzonitrile (selected because of the easier isolation of the amine as an ammonium salt) was performed under the standard conditions by using *i*PrOH-d_8 as the solvent. Phenyl methanammonium chloride was isolated in 95% yield. The ^{1}H NMR analysis of this product reveals a possible deuterium incorporation of 15% at the benzylic carbon, and in the $^{13}C\{^1H\}$ NMR spectrum, no C–D coupling is observed (Figure S1 in the Supporting Information). Taking into account all these data, it can be deduced that the

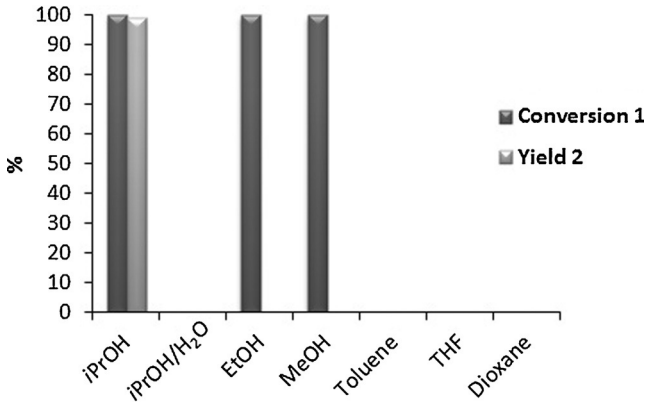


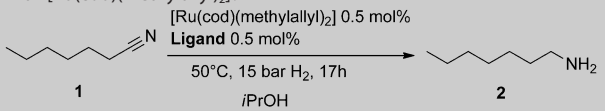
Figure 2. Influence of different solvents on 1-heptanenitrile **1** hydrogenation with [Ru(cod)(methylallyl)$_2$] and **L2** at 0.5 mol%, 50 °C, 15 bar H_2, 17 h.

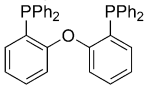
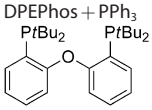
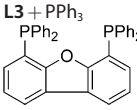
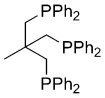
hydrogen transfer mechanism is not the major pathway of this reaction.

Next, several ruthenium precursors in combination with **L2** were evaluated for the hydrogenation of 1-heptanenitrile **1** under the optimal reaction conditions (Table S1 in the Supporting Information). Remarkably, none of the ruthenium precursors tested, other than [Ru(cod)(methylallyl)$_2$], afforded any conversion. Apparently, ruthenium pre-catalysts containing either halide anions or Ru carbonyl species do not form the active catalyst under such mild conditions. As expected, no hydrogenation of 1-heptanenitrile **1** was observed using [Ru(cod)(methylallyl)$_2$] in the absence of **L2** (Table 1, entry 15).

It should be noted that all previously reported systems for nitrile hydrogenation using [Ru(cod)(methylallyl)$_2$] in combination with a monodentate or bidentate P-, PP- or PN- ligand, needed the presence of a basic additive to achieve high conversions and selectivities to the primary amine.[11c,f–h] To understand the improved activity of the present ligand, a comparison of the 1-heptanenitrile **1** hydrogenation without base in the presence of [Ru(cod)(methylallyl)$_2$] and different mono-, bi-, and tridentate phosphines was performed (Table 2).

Table 2. Ligand screening in the hydrogenation of 1-heptanenitrile 1 with [Ru(cod)(methylallyl)$_2$].[a]

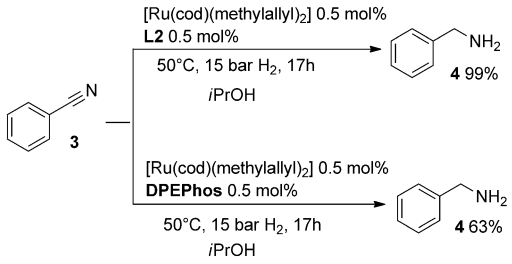


Entry	Ligand	Conv. [%][b]	Yield **2** [%][b]
1[c]	PPh_3	26	24
2[c]	$PtBu_3$	24	19
3	 **DPEPhos**	98	93
4[d]	DPEPhos + PPh_3	95	91
5	 **L3**	20	13
6[d]	**L3** + PPh_3	10	6
7	 **L4**	27	24
8	 **Triphos**	73	62
9	**L1**	23	15
10	**L2**	100	>99

[a] Standard reaction conditions: 1-heptanenitrile (0.5 mmol, 55.6 mg), [Ru(cod)(methylallyl)$_2$] (0.5 mol%), ligand (0.5 mol%), dry *i*PrOH (2 mL), 15 bar H_2, 17 h. [b] Conversion of **1** and yield of **2** were calculated by GC by using hexadecane as an external standard. [c] Ligand (1.5 mol%). [d] Each ligand was used at 0.5 mol%.

Monodentate phosphines at 1.5 mol%, for example, PPh_3 and $PtBu_3$, did not promote the hydrogenation of 1-heptanenitrile **1** efficiently, giving heptyl amine **2** in low yields (Table 2, entries 1 and 2). In contrast, the commercially available bidentate ligand bis-[2-(diphenylphosphino)phenyl]ether (DPEPhos) afforded heptyl amine **2** in high yields (Table 2, entry 3), whereas its *tert*-butyl analog only gave the amine in low yields (Table 2, entry 5). For a better comparison with the tridentate phosphines, the combinations of bidentate ligands DPEPhos and **L3** with PPh_3 (each ligand at 0.5 mol%) were tested; these results showed no significant differences with respect to the catalytic tests with the bidentate ligands (Table 2, entries 4 and 6). In addition, a rigid analogue of DPEPhos, 4,6-bis(diphenylphosphino)dibenzofuran **L4**, only gave low yields of heptyl amine **2** (24%, Table 2, entry 7). Among the tridentate phosphines tested (Table 2, entries 8–10), **L2** resulted in the highest activity and gave much better results than the commercially available 1,1,1-tris(diphenylphosphinomethyl)ethane (triphos).

Then, the ability of the most active systems, [Ru(cod)(methylallyl)$_2$] with DPEPhos and **L2**, to hydrogenate aromatic nitriles was studied by employing benzonitrile **3** as benchmark substrate (Scheme 2). By using the optimized conditions for 1-heptanenitrile (Table 1, entry 10), excellent yields of benzyl amine **4** were found in the case of **L2**, whereas DPEPhos only gave the amine in moderate yields (63%). Taking into account this result, further studies were continued using only **L2** as the ligand.



Scheme 2. Comparison of benzonitrile hydrogenation with [Ru(cod)(methylallyl)$_2$] in the presence of **L2** or DPEPhos.

Remarkably, the novel [Ru(cod)(methylallyl)$_2$]/**L2** combination allowed for hydrogenation of both aromatic and aliphatic nitriles under mild reaction conditions (50 °C, 15 bar H_2, and 0.5 mol%), affording good yields of the corresponding amines. For a deeper understanding of this process, we decided to perform a comparative study of the yield versus time profiles of the hydrogenation of an aromatic nitrile, an aliphatic nitrile, and the combination of both. Figure 3 shows the results corresponding to the hydrogenation of benzonitrile **3** (a), 1-octanenitrile **5** (b, selected for analytical reasons), and the mixture of both substrates (c). Figure S2 (in the Supporting Information) shows a more detailed graph of the corresponding initial rates of each experiment. A comparison of the benzonitrile and 1-octanenitrile plots shows that the $[TOF]_0$ value (turnover frequency at initial times, calculated as $[r_0 \times (mol\%)^{-1}]$ where r_0 is the slope of the linear equation: yield (%) $= r_0 \times$ time (h), de-

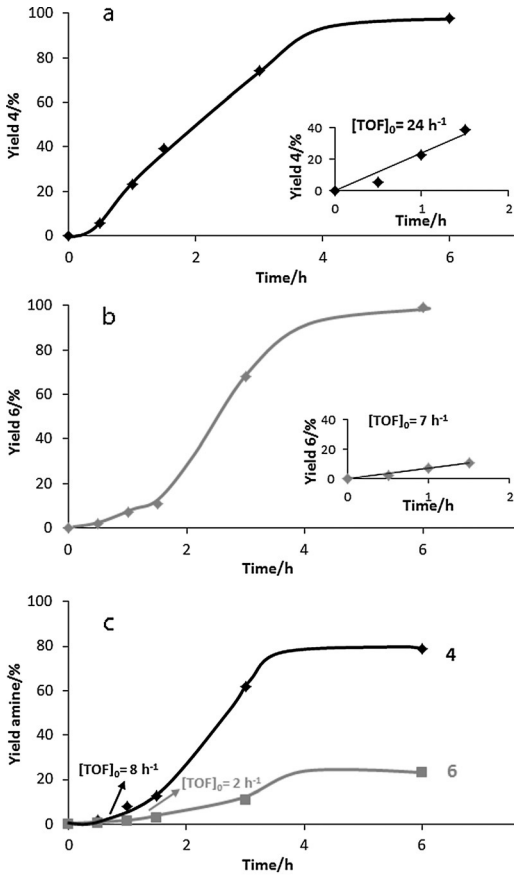


Figure 3. Yield versus time kinetic profiles using [Ru(cod)(methylallyl)$_2$]/**L2** 1 mol%, at 50 °C, 15 bar H_2, 6 h for: a) benzonitrile **3** hydrogenation to benzyl amine **4**; b) 1-octanenitrile **5** hydrogenation to octyl amine **6**; c) concomitant benzonitrile **3** and 1-octanenitrile **5** hydrogenation. Insets for a and b correspond to the initial rates plots in which $[TOF]_0$ is calculated as $[r_0 \times (\text{mol}\%)^{-1}]$ where r_0 is the slope of the linear equation: yield (%) = $r_0 \times$ time (h) defined at initial reaction times. Figure S1 (in the Supporting Information) shows the initial rates for all the experiments.

fined at initial reaction times) for the aromatic nitrile is approximately 3.5 times higher than the value for the aliphatic one. Interestingly, in the experiment performed with both nitriles (Figure 3c), although the hydrogenation rates for both compounds decreased, the ratio between the $[TOF]_0$ values corresponding to each substrate is very similar, being four times higher for the aromatic nitrile with respect to the aliphatic one. These results clearly demonstrate that the studied catalytic system is more active for the hydrogenation of aromatic nitriles than for aliphatic ones.

With the aim of gaining mechanistic clues about the catalytic system, a yield versus time profile of the hydrogenation of 1-octanenitrile was performed after preactivation of the [Ru(cod)(methylallyl)$_2$]/**L2** combination with H_2 (Figure S2a in the Supporting Information). Under these conditions, the induction period was significantly mitigated, indicating that a Ru–hydrido complex could be an active species in the catalytic cycle. Moreover, the prevention of the induction period was also observed when the hydrogenation of 1-octanenitrile was performed in the presence of 10 mol% KO*t*Bu (Figure S3b in the Supporting Information).

Finally, the general applicability of the methodology was evaluated through the hydrogenation of a series of aromatic and aliphatic nitriles (Table 3). For the majority of substrates, good yields of the corresponding primary amines were obtained at 50 °C by using 15 bar of H_2. Electron-releasing (Table 3, entries 2–6) as well as electron-withdrawing (Table 3, entries 7–9) substituted benzonitriles were successfully hydrogenated with the [Ru(cod)(methylallyl)$_2$]/**L2** system, although higher catalyst loadings were needed (2 mol%) in the latter case. Interestingly, ester and amido functionalities were also tolerated (Table 3, entries 10 and 11) and the corresponding amines were isolated in high yields. However, slightly higher temperatures (70 °C for methyl 4-cyanobenzoate and 100 °C for *N*-(4-cyanophenyl)acetamide) and 2 mol% catalyst loading were required for these examples. Furthermore, thiophene-2-carbonitrile could also be hydrogenated at mild conditions by using 2 mol% catalyst (Table 3, entry 12).

Then, a series of aliphatic nitriles was tested by using the [Ru(cod)(methylallyl)$_2$]/**L2** system (Table 3, entries 13–20) at 50 °C, with 15 bar of H_2, and 0.5 mol% catalyst loading. Under these conditions, aliphatic nitriles bearing a short alkyl chain afforded the corresponding amines in high yields (Table 3, entries 13–15). In contrast, substrates with longer alkyl chains (Table 3, entries 16 and 17) or branched (Table 3, entry 18), needed either higher catalyst loadings (1 mol%) or temperatures (70 °C) to be successfully hydrogenated, which is probably due to the major steric hindrance of these substrates. Finally, cyclic nitriles (Table 3, entries 19 and 20) were converted into the corresponding primary amines at mild conditions, too.

In comparison with the already described Ru base-free systems for the hydrogenation of nitriles, most of which are based on pincer complexes operating in a temperature range between 90 and 135 °C,[11a,b,d] the [Ru(cod)(methylallyl)$_2$]/**L2** system presents the advantage of being able to hydrogenate a broad range of substrates at 50 °C.

Conclusions

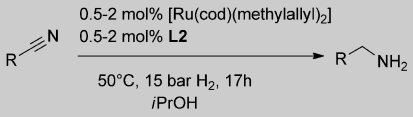
We have described a novel catalytic system based on the combination of [Ru(cod)(methylallyl)$_2$] and ligand **L2** for the selective hydrogenation of nitriles to primary amines. This new protocol presents the advantage of not needing any basic additive to achieve good selectivities to the primary amine. Furthermore, a variety of aromatic and aliphatic nitriles can be hydrogenated at mild conditions (50 °C, 15 bar H_2).

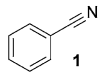
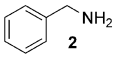
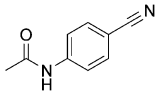
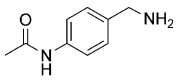
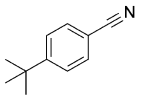
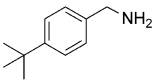
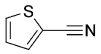
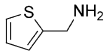
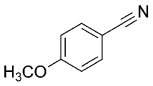
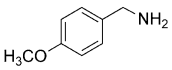
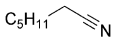
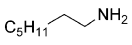
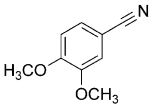
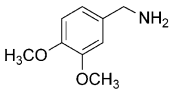
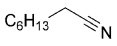
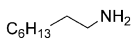
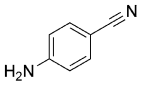
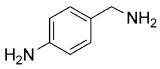
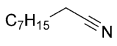
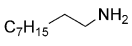
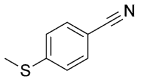
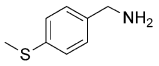
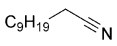
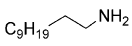
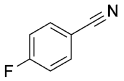
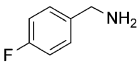
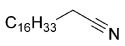
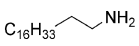
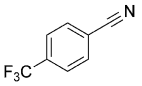
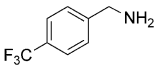
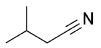
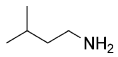
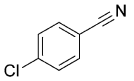
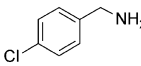
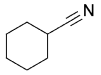
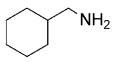
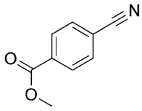
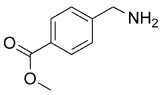
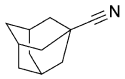
Experimental Section

General procedure for nitrile hydrogenation with [Ru(cod)(methylallyl)$_2$]/L2

A 4 mL glass vial containing a stirring bar was charged with [Ru(cod)(methylallyl)$_2$] (0.8 mg, 0.0025 mmol, 0.5 mol%) and **L2** (1.5 mg, 0.0025 mmol, 0.5 mol%). The vial, sealed with a septum equipped with a syringe needle, was evacuated and subsequently flushed with argon three times. Dry isopropanol (2 mL) and the corresponding nitrile (0.5 mmol) were added under argon. The vial was set in an alloy plate and introduced into a 300 mL autoclave

Table 3. Hydrogenation of various nitriles.[a]



Entry	Nitrile	Amine	Cat. [mol%]	Conv. [%][b]	Yield [%][b]	Entry	Nitrile	Amine	Cat. [mol%]	Conv. [%][b]	Yield [%][b]
1	 **1**	 **2**	0.5	>99	96[c]	11[e]			2	>99	81[c]
2			0.5	>99	90	12			2	>99	76
3			0.5	>99	94	13			0.5	>99	82
4			0.5	>99	86	14			0.5	>99	99
5			0.5	>99	99	15			0.5	>99	97
6			1	>99	94[c]	16			1	>99	81
7			2	>99	88	17[d]			0.5	>99	72[c]
8			2	>99	75	18			1	>99	82
9			2	>99	97	19			0.5	>99	95
10[d]			2	>99	80[c]	20			0.5	>99	89

[a] Standard reaction conditions: nitrile (0.5 mmol), $[Ru(cod)(methylallyl)_2]$ (0.5–2 mol%), **L2** (0.5–1 mol%), dry *i*PrOH (2 mL), 15 bar H_2, 50 °C, 3 h. [b] Conversion and yields were calculated by GC by using hexadecane as an external standard. [c] Isolated yield as ammonium salt. [d] The reaction was performed at 70 °C. [e] The reaction was performed at 100 °C.

filled with argon. The autoclave was sealed, purged (20 bar H_2, three times), and pressurized with H_2 (15 bar). Then, the autoclave was seated in an aluminum block on a magnetic stirrer and heated to 50 °C for 17 h. After that, the reaction mixture was cooled in cold water and the gas carefully released. The reaction mixture was analyzed by GC-MS and GC with *n*-hexadecane as an internal standard.

Isolation of reaction products as the HCl salts

HCl (1 M in MeOH, 1 mL) was added to the reaction mixture and stirring was maintained for 30 min at room temperature. Then, the reaction mixture was transferred to a 100 mL round-bottom flask containing 50 mL of diethyl ether. The resulting precipitate was filtered and washed with diethyl ether and ethyl acetate.

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Keywords: amines · hydrogenation · nitriles · phosphine ligands · ruthenium

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