

# A General and Environmentally Benign Catalytic Reduction of Nitriles to Primary Amines

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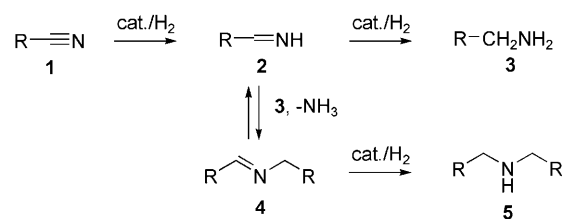
Dedicated to Professor Günther Oehme on the occasion of his 70th birthday

A vast number of amines are produced by both the bulk and fine chemical industries, and a plethora of naturally occurring nitrogen compounds, such as alkaloids, amino acids, and nucleotides, play a pivotal role in biological processes.<sup>[1]</sup>

During recent decades, several novel catalytic methods have been established for the synthesis of amines, such as palladium-catalyzed amination of aryl halides,<sup>[2]</sup> hydroaminations<sup>[3]</sup> and hydroaminomethylation of olefins or alkynes,<sup>[4]</sup> and homogeneous reductive aminations.<sup>[5]</sup> Nevertheless, the development of new and improved methods for the efficient and selective production of amines continues to be a challenging goal. Among the different known methods used, reductions are probably the most important due to the availability of starting materials (aldehydes, ketones, amides), price (hydrogen), and high atom efficiency. In this respect, the catalytic hydrogenation of nitriles also offers an interesting means of access to amines, which is used in industry for several products. In organic synthesis, nitriles are commonly reduced with stoichiometric amounts of metal hydrides, or in the presence of heterogeneous catalysts based on Pd, Ni, Co, etc. The former approach is expensive and not environmentally benign (over-stoichiometric amounts of waste), whereas the latter has limitations with respect to functional group tolerance and the excess of ammonia needed for high chemoselectivity. Surprisingly, the homoge-

nously catalyzed hydrogenation of nitriles has been scarcely investigated, in comparison with C=C–N, C=N, and NO<sub>2</sub> reductions.<sup>[6]</sup> More specifically, homogeneous reductions in the presence of few ruthenium,<sup>[7]</sup> rhodium,<sup>[8]</sup> and iridium<sup>[9]</sup> complexes are known. Notably, all these catalysts reveal the formation of significant amounts of side products, such as secondary amines and imines, which lower the selectivity and the overall yield of the desired primary amines. This is also a typical problem associated with heterogeneous catalysts. Interestingly, an improvement in primary amine selectivity was reported by Hidai and co-workers when the hydrogenation was carried out with ruthenium complexes tailored with bis(diarylamido)thioether ligands in the presence of catalytic amounts of base.<sup>[10]</sup>

As shown in Scheme 1, the chemoselectivity of the overall hydrogenation should be improved by using catalysts with activity towards imine **2** and/or by addition of ammonia, which shifts the equilibrium between **2** and **4** towards **2**.<sup>[11]</sup>



Scheme 1. Selectivity in the catalytic reduction of nitriles.

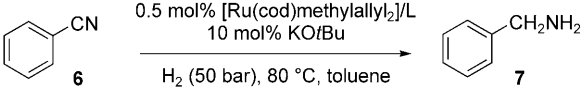
Herein, we describe for the first time the successful application of an easy-to-adopt catalytic system formed from commercially available [Ru(cod)methylallyl]<sub>2</sub> (cod = 1,5-cyclooctadiene) and DPPF (1,1'-bis(diphenylphosphino)ferrocene) for the homogeneous hydrogenation of a variety of aromatic and aliphatic nitriles, with excellent catalyst activity and high chemoselectivity.

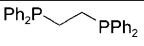
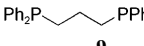
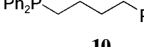
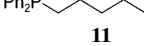
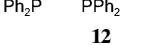
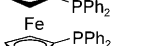
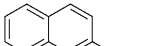
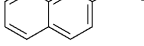
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Initial studies on the influence of reaction conditions were carried out with benzonitrile **6** as the model substrate by using 0.5 mol% ruthenium catalyst and 10 mol% base (potassium *tert*-butoxide) in toluene with an initial hydrogen pressure of 50 bar at 80 °C. All hydrogenation reactions were performed in an 8-fold parallel reactor array with a reactor volume of 3.0 mL.<sup>[12,13]</sup> Because the influence of ligands on homogeneous catalysis is crucial, we first examined the effect of several bidentate phosphorus-containing ligands (shown in Table 1; ligand abbreviations used herein:

Table 1. Influence of the ligand structure in the ruthenium-catalyzed reduction of benzonitrile.<sup>[a]</sup>



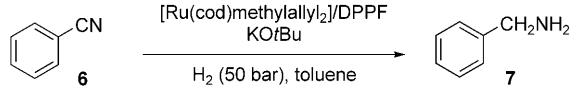
Entry	Ligand	Time <sup>[b]</sup> [h]	Yield <sup>[c]</sup> [%]	TOF <sup>[d]</sup> [h <sup>-1</sup> ]
1		24	34	3
2		6	35 (>99)	12
3		1	21	42
4		1 (24)	86 (99)	172
5		24	93	8
6		1	>99	>200
7		6 (24)	62 (>99)	21
8		24	91	9

[a] L=ligand. Reactions were carried out at 80 °C for 24 h with [Ru(cod)methylallyl]<sub>2</sub> (0.0019 mmol), ligand (0.0019 mmol), KOtBu (0.038 mmol), and benzonitrile (0.38 mmol) in toluene (2.0 mL) under hydrogen (50 bar). [b] The yield after 24 h is given in parentheses. [c] The yield was determined by GC (30 m HP Agilent Technologies column, 50–300 °C; benzonitrile: 7.08 min, benzylamine: 7.60 min) with nitrobenzene as the internal standard. [d] Turnover frequencies (TOFs) based on stated reaction time.

DPPPe = 1,5-bis(diphenylphosphino)pentane, DPPPB = 1,4-bis(diphenylphosphino)butane, DPPPP = 1,3-bis(diphenylphosphino)propane, DPPE = 1,2-bis(diphenylphosphino)ethane). To our delight, in most cases excellent chemoselectivity (>99%) was attained. The best catalyst activity (>99% yield within 1 h) was observed with DPPPF as the

ligand (Table 1, entry 6). A DPPPe-based system also gave a high yield (86%) of benzylamine within 1 hour (Table 1, entry 4). The catalyst performance dropped with decreasing carbon chain length in the chelating ligands in the following order: DPPPe > DPPPB > DPPPP > DPPE (Table 1, entries 1–4). Phosphorus ligands with a rigid or sterically demanding backbone (Table 1, entries 7 and 8) gave complete reduction of benzonitrile at longer reaction times (24 h). Next, the catalyst performance of the [Ru(cod)methylallyl]<sub>2</sub>/DPPPF was studied in more detail. Decreasing the reaction time to 10 min still led to a 93% yield of benzylamine, which corresponds to a catalyst TOF of 1116 h<sup>-1</sup> (Table 2, entry 2).

Table 2. Reduction of benzonitrile by using an in situ ruthenium/DPPPF catalyst.<sup>[a]</sup>



Entry	Catalyst [mol %]	Base [mol %]	T [°C]	t [min]	Yield <sup>[b]</sup> [%]	TOF <sup>[c]</sup> [h <sup>-1</sup> ]
1	0.25	20	40	1440	88	–
2 <sup>[d]</sup>	0.50	20	80	10	93	1116
3	0.50	–	80	10	10	120
4	0.25	10	80	10	79	1896
5	0.25	20	80	10	66	1590
6	0.125	20	80	10	10	495
7	0.125	20	100	10	21	1012
8	0.125	20	120	10	99	4752
9	0.125	20	140	10	>99	4800
10	0.06	20	140	10	60	5783
11	0.03	20	140	10	3	578

[a] Reactions were carried out for the given time at temperatures of 40–140 °C in toluene (2.0 mL) under hydrogen (50 bar). [b] The yield was determined by GC (30 m HP Agilent Technologies column, 50–300 °C; benzonitrile: 7.08 min, benzylamine: 7.60 min) with nitrobenzene as the internal standard. [c] TOFs based on stated reaction time. [d] [Ru(cod)methylallyl]<sub>2</sub> (0.0019 mmol), ligand (0.0019 mmol), KOtBu (0.076 mmol), and benzonitrile (0.38 mmol).

It is worth noting that at lower catalyst loading (0.125 mol%), full conversion and excellent yield (>99%) are obtained within 10 min, albeit at higher temperatures (120–140 °C; Table 2, entries 8, 9). The highest TOF (5783 h<sup>-1</sup>) observed for this reaction to date was obtained at 140 °C with 0.06 mol% catalyst loading (Table 2, entry 10).

It is important to note that even at low temperature (40 °C) the catalyst showed good activity and selectivity (Table 2, entry 1).<sup>[14]</sup> In contrast with most heterogeneously catalyzed reductions of nitriles, there is no need to add ammonia to this system.

After demonstrating the advantages of the Ru/DPPPF system for the hydrogenation of benzonitrile, we examined a number of substrates under optimized reaction conditions (80 °C, 1 h, 50 bar).

As shown in Table 3, eighteen different nitriles were successfully hydrogenated with excellent chemoselectivity to give the corresponding primary amines within 1 to 2 h.

Table 3. Scope and limitations of the ruthenium catalyst.<sup>[a]</sup>

Entry	Substrate	T [°C]	t [h]	Yield <sup>[b]</sup> [%]
1		80	1	99
2		80 140	1 1	85 92
3		80 140	1 1	86 87
4		140	1	69
5		80	1	86
6		80	1	98
7		80	1	78 <sup>[c]</sup>
8		80 140	2 2	46 95
9		80	1	93
10		140	1	86
11		80	2	92
12		140	2	84
13		140	2	99
14		140	1	79
15		80	1	63
16		80 140	2 2	60 98
17		140	2	91 <sup>[d]</sup>
18		140	2	87 <sup>[d]</sup>

[a] Reactions were carried out at 80 or 140 °C for either 1 h with [Ru(cod)methylallyl]<sub>2</sub> (0.0019 mmol), ligand (0.019 mmol), KOtBu (0.038 mmol), nitrile (0.38 mmol), and toluene (2.0 mL) in an 8-fold parallel autoclave or 2 h with [Ru(cod)methylallyl]<sub>2</sub> (0.019 mmol), ligand (0.019 mmol), KOtBu (0.38 mmol), nitrile (3.8 mmol), and toluene (20 mL) in a 50 mL Parr autoclave. [b] The yield was determined by GC (30 m HP Agilent Technologies column, 50–300 °C) with diglyme as the internal standard. [c] Isolated yield. [d] 10 mol % NH<sub>4</sub>Cl was added.

Thereby, the [Ru(cod)methylallyl]<sub>2</sub>/DPPF catalyst system exhibited a broad functional group tolerance. For example, amino-, ester-, and bromo-substituted benzonitriles gave the corresponding benzylamines in yields of 69–98% (Table 3, entries 4, 6, and 7). When aromatic nitriles with electron-withdrawing or electron-donating substituents were used, no general trend on the reactivity was found. Both electron-deficient (Table 3, entries 2 and 6) and electron-rich compounds (Table 3, entry 3) showed high reactivity and selectivity. If the results for the *ortho*- and *para*-substituted methoxybenzonitriles (Table 3, entries 5 and 10) are compared, it can be seen that the sterically hindered substrate needed a higher temperature for a similar hydrogenation result. The potential of the catalyst is demonstrated by applying more challenging heterocyclic and alkyl nitriles. Although in some cases (Table 3, entries 12–14) a higher reaction temperature was required, to the best of our knowledge these are the first examples in which heterocyclic nitriles were successfully hydrogenated in high yields within 1–2 h. Finally, the catalytic system [Ru(cod)methylallyl]<sub>2</sub>/DPPF was also adapted for the reduction of aliphatic nitriles (Table 3, entries 17 and 18). Here, the addition of 10 mol % of NH<sub>4</sub>Cl proved to be necessary for the hydrogenation process to occur. For example, 2-phenethylamine is produced from readily available benzyl cyanide in 91% yield.

In summary, an easily accessible in situ catalyst composed of [Ru(cod)methylallyl]<sub>2</sub> and DPPF has been developed for the environmentally benign hydrogenation of various nitriles to give primary amines. Under optimized conditions, a superior catalyst activity with a TOF of up to 5783 h<sup>-1</sup> has been achieved in the model reaction. The general applicability and functional group tolerance of the presented system is shown in the reduction of 18 different aromatic and aliphatic nitriles.

## Experimental Section

**General procedure:** A solution of benzonitrile (0.38 mmol) in toluene (1.0 mL) was transferred by syringe into an autoclave that contained KOtBu (0.038 mmol) and argon. The catalyst was generated in situ by stirring [Ru(cod)methylallyl]<sub>2</sub> (0.0019 mmol) and DPPF (0.0019 mmol) in toluene (1.0 mL) for 10 min and afterwards transferring the solution by syringe into the autoclave. Then hydrogen (50 bar) was added to the autoclave and the mixture was stirred for 1 h at 80 °C. After the predetermined time, the hydrogen was released and nitrobenzene or diglyme were added as internal standards. After stirring for 10 min, the reaction mixture was filtered through a short plug of silica gel. The yield was measured by GC (30 m HP Agilent Technologies column, 50–300 °C, benzonitrile: 7.08 min, benzylamine: 7.60 min).

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**Keywords:** homogeneous catalysis • hydrogenation • nitriles • P ligands • primary amines • ruthenium

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