



## Ruthenium N-heterocyclic carbene catalysts for selective reduction of nitriles to primary amines

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### ABSTRACT

Easily accessible in situ catalysts composed of  $[\text{Ru}(\text{cod})(2\text{-methylallyl})_2]$  and N-heterocyclic carbene ligands have been developed for the environmentally benign hydrogenation of various nitriles to give primary amines. Applying optimized conditions in the presence of  $\text{SIMesBF}_4$  as ligand high catalyst activity of up to  $392 \text{ h}^{-1}$  is achieved in the hydrogenation of benzonitrile. The general applicability and functional group tolerance of this novel catalyst system are shown in the reduction of ten different nitriles.

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Amines constitute important bulk and fine chemicals as well as pharmaceuticals. Moreover, nitrogen-based compounds represent precursors for alkaloids, amino acids, and nucleotides, which play a key role in manifold natural processes.<sup>1</sup> During the last decades efficient catalytic C–N bond forming methods were developed, for example, palladium-catalyzed amination of aryl halides,<sup>2</sup> hydroamination,<sup>3</sup> and hydroaminomethylation of olefins or alkynes.<sup>4</sup> In addition, the reduction of carbonyl groups,<sup>5</sup> and amides or nitriles offers an attractive access to amines.

In recent years we have developed novel and improved catalysts for the synthesis of benzonitriles.<sup>6,7</sup> It is well known that these nitriles can be reduced with (over)stoichiometric amounts of metal hydrides, for example,  $\text{LiAlH}_4$  or in the presence of heterogeneous catalysts based on Pd, Ni, Co, etc. However, the catalytic hydrogenation of nitriles in the presence of homogeneous metal complexes has been scarcely investigated compared to C=C, C=O, and C=N bond reductions.<sup>8</sup> Nevertheless, few examples of nitrile reductions are known with ruthenium,<sup>9</sup> rhodium,<sup>10</sup> and iridium<sup>11</sup> complexes. In this context, last year we have reported ruthenium phosphine catalysts based on  $\text{dppf}^{12}$  or  $\text{PPH}_3^{13}$  for the hydrogenation of aromatic nitriles to give primary amines with high chemoselectivity (>99%). More recently, we also became interested in the potential applicability of carbene ligands in ruthenium-catalyzed hydrogenations.<sup>14</sup> Since Arduengo et al.<sup>15</sup> introduced the first stable N-heterocyclic carbenes in the early 1990s this class of ligands has become increasingly popular in cataly-

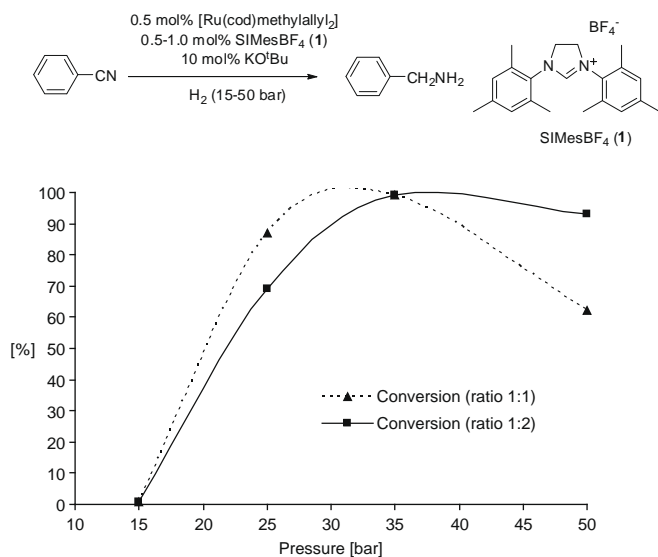
sis.<sup>16,17</sup> Compared to tertiary phosphines NHC ligands are characterized by a stronger metal–interaction and a minimized ligand dissociation.

Herein, we describe for the first time catalytic hydrogenations of nitriles to primary amines in the presence of carbene ligands. Our initial studies were carried out with benzonitrile as standard substrate using 0.5 mol% of  $[\text{Ru}(\text{cod})(2\text{-methylallyl})_2]$  and 0.5–1.0 mol% of 1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazolium tetrafluoroborate ( $\text{SIMesBF}_4$ ) as in situ catalyst in the presence of 10 mol% of base. All exploratory hydrogenation reactions were performed in an eightfold parallel reactor array with a reactor volume of 3.0 mL.<sup>18</sup> The first set of reactions was run in toluene with various hydrogen pressures at 80 °C at a Ru: $\text{SIMesBF}_4$  ratio of 1:1 and 1:2, respectively. To our delight full conversion and excellent chemoselectivity (>99%) are obtained with this novel carbene-based catalyst. As depicted in Figure 1, the optimal hydrogen pressure depends on the ratio of Ru: $\text{SIMesBF}_4$ . Notably, best results are obtained at 30–35 bar of hydrogen, which is significantly lower compared to similar hydrogenations in the presence of Ru/phosphine catalysts.<sup>13,14</sup>

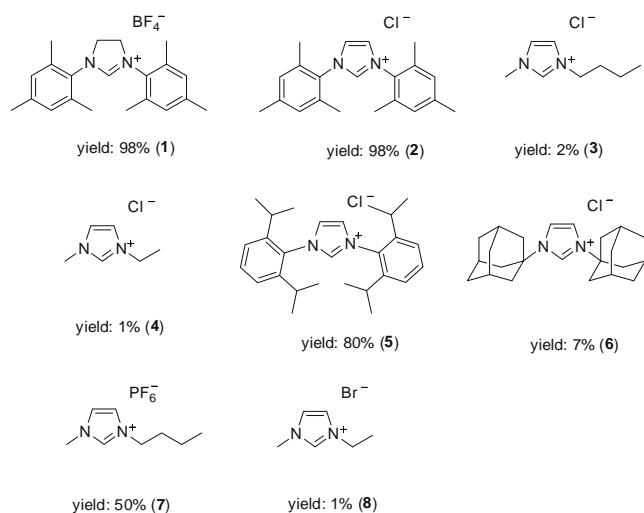
Next, we tested various imidazolium salts shown in Scheme 1 as carbene precursors to investigate the influence of the ligand structure on the outcome of the reaction. The best catalyst performance is observed in the presence of the mesitylene-based imidazolium salts **1** and **2**.

Increasing the bulkiness in 2,6-position of the aryl substituent by *iso*-propyl groups gave decreased conversion (Scheme 1, **5**). A further depletion of the yield of benzyl amine is observed by changing the N-substituent from aryl to alkyl (Scheme 1, **3**, **4**, **8**).

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**Figure 1.** Influence of pressure at different ligand:metal ratios (reaction conditions: 80 °C, 1 h, 0.0038 mmol [Ru(cod)(2-methylallyl)<sub>2</sub>], 0.0038 or 0.0076 mmol SIMesBF<sub>4</sub>, 10 mol % KO<sup>t</sup>Bu, 0.76 mmol benzonitrile in 2.0 mL toluene).

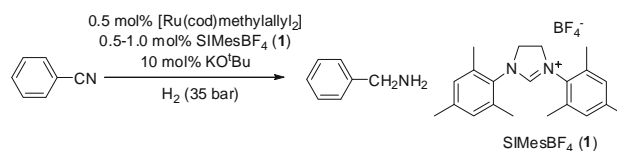


**Scheme 1.** Different ligands tested in the ruthenium-catalyzed reduction of benzonitrile (reaction conditions: 80 °C, 1 h 0.0038 mmol [Ru(cod)(2-methylallyl)<sub>2</sub>], 0.0038 mmol carbene, 10 mol % KO<sup>t</sup>Bu, 0.76 mmol benzonitrile in 2.0 mL toluene at 35 bar hydrogen atmosphere).

However, in the presence of the simple precursor **7**, the desired product is still obtained in 50% yield. In order to find optimal reaction conditions, the influence of temperature and catalyst concentration on the selectivity and yield was also investigated (Table 1). Applying the catalyst composed of [Ru(cod)(2-methylallyl)<sub>2</sub>] and imidazolium salt **1** excellent yield (98%) and chemoselectivity (>99%) are observed even at 40 °C (Table 1, entries 3 and 4). On the other hand at 80 °C a TOF of 392 h<sup>-1</sup> (Table 1, entry 6) is observed, which reflects an increase in catalytic efficiency by the factor ten compared to the Ru/PPh<sub>3</sub> system.<sup>13</sup>

Finally, we performed the reduction of different nitriles under optimized conditions to demonstrate the scope and limitations of the Ru/carbene catalyst (Table 2).<sup>19</sup> It is important to note that in all cases excellent chemoselectivity with more than 99% of the corresponding primary amine is obtained, except for *p*-bromobenzonitrile (Table 2, entry 2), where a small amount of the diamine is detected. In general, the hydrogenation of substituted benzonitriles proceeded in good to excellent yields under mild conditions

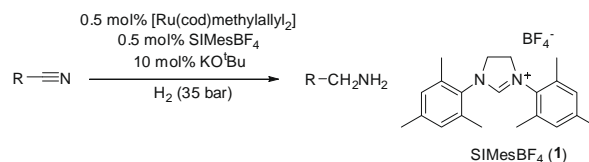
**Table 1**  
Screening of reaction temperature and reaction time<sup>a</sup>



Entry	Cat. (mol %)	T (°C)	T (h)	Yield (%)	Chemoselectivity (%)
1	0.5	20	2	5	99
2	0.5	40	2	28	98
3	0.5	40	6	98	99
4	0.5	40	16	98	99
5	0.5	60	2	97	99
6	0.5	80	0.5	99	99
7	0.5	80	1	>99	>99
8	0.25	80	1	95	99
9	0.125	80	1	37	99
10	0.06	80	1	12	99

<sup>a</sup> Reaction conditions: 20–80 °C, 0.5–16 h, 0.038 mmol [Ru(cod)(2-methylallyl)<sub>2</sub>], 0.038 mmol SIMesBF<sub>4</sub>, 10 mol % KO<sup>t</sup>Bu, 7.6 mmol benzonitrile in 20.0 mL toluene under 35 bar hydrogen atmosphere in a 50 mL Paar autoklave.

**Table 2**  
Scope and limitation of catalyst<sup>a</sup>



Entry	Substrate	T (°C)	T (h)	Yield (%)	Sel. (%)
1		80	1	>99	>99
2		40	6	41	>99
		140	1	36	74 <sup>c</sup>
3		80	1	78	98
4		40	6	29	>99
		40	16	99	>99
5		40	16	92	>99
		80	1	87	>99
6		40	6	>99	>99
7		40	16	15	>99
		60	6	31	>99
8		40	6	—	—
		80	1	10	>99
9		80	1	28	>99
10 <sup>b</sup>		80	1	12	>99

<sup>a</sup> Reaction conditions: 40–140 °C, 1–16 h, 0.038 mmol [Ru(cod)(2-methylallyl)<sub>2</sub>], 0.038 mmol SIMesBF<sub>4</sub>, 10 mol % KO<sup>t</sup>Bu, 7.6 mmol nitrile in 20.0 mL toluene under 35 bar hydrogen atmosphere.

<sup>b</sup> 10 mol % NH<sub>4</sub>Cl.

<sup>c</sup> 26% of the corresponding diamine.

(40–80 °C) within 6–16 h. Especially electron-rich aryl nitriles are suitable substrates (Table 2, entries 1–6) for this reaction. Apparently, the substrate scope of the parent Ru/carbene catalyst is lower compared to the Ru/phosphine systems.<sup>12,13</sup> Hence, reduction of heteroarylnitriles and 3-phenylpropionitrile gave the corresponding primary amines in low yield (Table 2, entries 8–10).

In summary, we demonstrated for the first time the possibility to apply ruthenium/carbene catalysts for the hydrogenation of various nitriles. While the substrate scope of these catalysts should be further improved, good yields and excellent chemoselectivity are obtained for the hydrogenation of different benzonitriles at ambient temperature (40 °C) and pressure.

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- Institute of Automation (IAT), Richard Wagner Str. 31/H. 8, 18119 Rostock-Warnemünde, Germany.
- General reaction procedure*: A solution of benzonitrile (0.38 mmol) in toluene (1.0 mL) was transferred by syringe into an autoclave that contained KO<sup>t</sup>Bu (0.038 mmol) and argon atmosphere. The catalyst was generated in situ by stirring [Ru(cod)(2-methylallyl)]<sub>2</sub> (0.0019 mmol) and the carbene ligand (0.0019 mmol) in toluene (1.0 mL) for 10 min and afterwards transferring the solution by syringe into the autoclave. Then hydrogen (35 bar) was added to the autoclave and the mixture was stirred for the respective time at 40–80 °C. After the predetermined time, the hydrogen was released and nitrobenzene or diglyme was 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).