Catalysis
Science &
Technology

COMMUNICATION

View Article Online
View Journal

Cite this: DOI: 10.1039/c6cy00834h

Received 18th April 2016,
Accepted 19th May 2016

DOI: 10.1039/c6cy00834h

www.rsc.org/catalysis

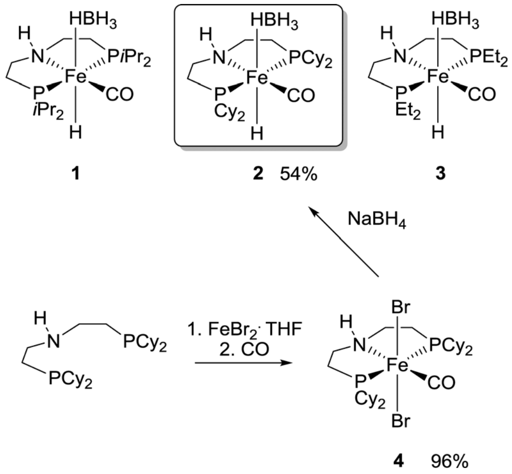
Selective catalytic hydrogenation of nitriles to primary amines using iron pincer complexes†

S. Lange,[a] S. Elangovan,[a] C. Cordes,[a] A. Spannenberg,[a] H. Jiao,[a] H. Junge,[a] S. Bachmann,[b] M. Scalone,[b] C. Topf,[a] K. Junge[a] and M. Beller*[a]

The selective catalytic hydrogenation of nitriles to primary amines with the well-defined Fe(PNP^{Cy}) pincer complex **2** is reported. This iron pincer catalyst shows superior catalytic activity and selectivity in the reduction of various nitriles including industrially relevant adipodinitrile in high yields under relatively mild conditions.

Primary amines constitute important building blocks in the agrochemical and pharmaceutical industries as well as for the manufacture of dyes, pigments, polymers and for gas treatment.[1] Compared to classic organic reactions, such as alkylation of ammonia and reductive amination, the reduction of nitriles represents an alternative way to form primary amines. Usually, stoichiometric amounts of metal hydride reagents are applied for nitrile reduction with high efficiency.[2] Due to the huge quantities of waste metal salts, these procedures are connected with economic and ecologic limitations. Therefore, catalytic transformation of nitriles with molecular hydrogen offers an atom-economic and environmentally benign alternative for the synthesis of amines.[3] Although heterogeneous metal catalysts are known for the reduction of nitriles, often they suffer from low to moderate selectivity and limited functional group tolerance under the required drastic conditions. Instead, homogeneous catalysts for the hydrogenation of nitriles are generally based on precious metals such as Ru,[4] Ir,[5] Rh,[6] Re[7] and Mo.[8] Recently, we developed the first homogeneous iron-based catalyst **1** for the selective reduction of a large number of aromatic, aliphatic and heterocyclic nitriles to the corresponding primary amines requiring no addition of base.[9] This iron-pincer complex **1** has been developed parallel in our group and in Schneider's group, showing extraordinary catalytic activities in various hydrogenation and dehydrogenation reactions.[10] Presently, the application of non-noble metal pincer complexes in homogeneous reactions is studied very intensively by the catalytic community.[11,12] Regarding the reduction of nitriles, until now, only two other examples of non-noble metal catalysts have been reported by the group of Milstein.[12*f*,*i*] Compared to iron catalyst **1**, the Co PNN as well as the Fe PNP pincer complexes seem to be less active, requiring addition of base, longer reaction time (16–48 h) and higher temperatures (135–140 °C). Thus, there is room for improvement. Herein, we evaluate the influence of alkyl substituents at the phosphorus binding site on the catalytic performance of the complexes in the hydrogenation of nitriles.‡ Therefore, we synthesized the new iron pincer complexes **2** and **3**, bearing different substituents on the phosphine moiety (Scheme 1).[13]

The synthesis of Fe(PNP^{Et}) complex **3** has been described,[10*i*] while we show here the preparation of Fe(PNP^{Cy}) **2**: first, the dibromo complex [(PNP^{Cy})Fe(CO)Br$_2$] **4** is produced by the treatment of FeBr$_2$·2THF with the PNP ligand, bis(2-dicyclohexyl phosphinoethyl)amine under an



Scheme 1 Structure of different Fe(PNP) catalysts **1**–**3** and synthesis of complex **2**.

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[a] *Leibniz-Institut für Katalyse e.V. an der Universität Rostock, Albert-Einstein-Straße 29a, 18059 Rostock, Germany. E-mail: matthias.beller@catalysis.de*

[b] *F. Hoffmann-La Roche AG, Process Research & Development, CoE Catalysis, 4070 Basel, Switzerland*

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c6cy00834h

atmosphere of CO.[14] Complex **4** is isolated as a dark blue solid compound in 96% yield, showing a singlet at δ = 61.2 ppm in the ^{31}P NMR spectra. In the IR spectra of **4**, a strong CO stretching band at 1943 cm^{-1} and an N–H vibration at 3117 cm^{-1} are observed. The hydridoborato complex **2** is prepared in 76% yield by the reaction of complex **4** with an excess of $NaBH_4$. The bright yellow complex **2** was characterized by different spectroscopic methods (NMR, IR, MS). In the ^{31}P NMR spectra of the dihydride complex **2**, a mixture of two isomers was detected at δ = 91.5 ppm (major isomer) and δ = 92.7 ppm (minor isomer).[15] Additionally, the ^{1}H NMR spectrum shows a sharp triplet at δ = −19.6 ppm (major isomer) for the hydride ligand, whereas the BH_4 ligand resonates as a broad signal at δ = −2.9 ppm. In the IR spectrum, bands at 1905 cm^{-1} indicate the coordination of CO to the metal centre. Furthermore, crystals suitable for X-ray diffraction analysis were obtained from a THF/*n*-heptane mixture. In the molecular structure of complex **2** shown in Fig. 1, the central iron atom is placed in a distorted octahedral coordination geometry.[16] The HBH_3 ligand and the N–H bond are arranged in the *cis* position. Moreover, the CO ligand and the N atom as well as the hydride ligand and the HBH_3 ligand are located *trans* to each other.

The reaction of benzonitrile to benzyl amine was chosen as a benchmark system to study the influence of structural variation of the phosphine moiety on the activity of this type of catalysts. In preliminary experiments, different amounts of catalyst loadings (0.25–1 mol%) of **1**–**3** were tested at 30 bar H_2, 3 h, 70 °C (Scheme 2). With 1 mol% catalyst concentration, all three complexes produced benzyl amine in high yields, while the catalytic performance of Fe(PNP^{Et}) complex **3** completely dropped down with half the amount of catalyst. This finding is in contrast to the results for the iron-catalysed ester reduction, where the Fe(PNP^{Et}) complex **3** is the most active one of these three catalysts.[10i] We were pleased that complex **2** afforded 90% yield of benzyl amine using 0.5 mol% catalyst concentration, 30 bar H_2 at 70 °C. Regarding the influence of the alkyl substituents at the phosphorus binding site on the catalytic efficiency of the three Fe pincer complexes **1**–**3**, the following sequence was found: Cy = iPr > Et.

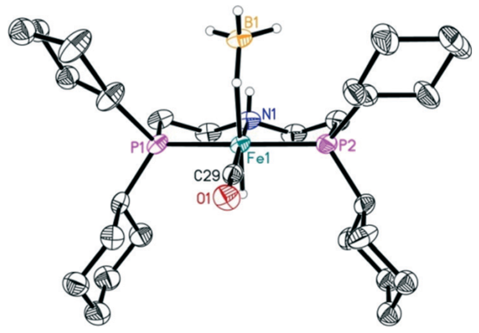
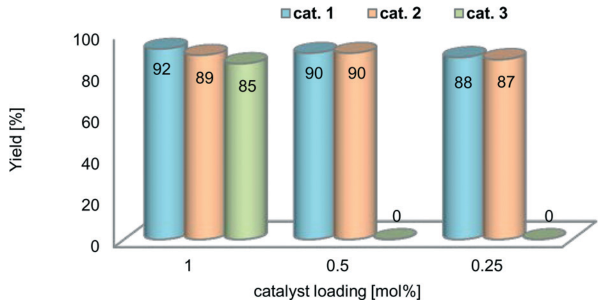


Fig. 1 Molecular structure of complex **2** in the crystal. Only one of the two molecules of the asymmetric unit is depicted. Displacement ellipsoids are drawn at the 30% probability level. Hydrogen atoms except those on Fe, N and B are omitted for clarity.

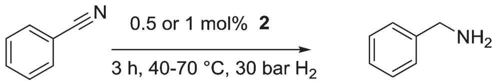


Scheme 2 Yield of benzyl amine using different catalyst loadings of **1**–**3**. Reaction conditions: 1.0 mmol of benzonitrile, *x* mol% **1**–**3**, 2 mL of iPrOH, 30 bar H_2, 3 h, 70 °C.

A short optimization of the reaction parameters (time, solvent, temperature) applying the new active complex **2** is summarized in Table 1. The temperature and the solvent play a significant role for the catalyst efficiency. Good to excellent yields of benzyl amine are produced with 0.5–1 mol% of **2** at 70 °C in 3 h (Table 1, entries 1 and 2). The reaction runs fast, yielding complete conversion and 86% of amine after 2 h. Interestingly, at temperatures below 70 °C there is still conversion of the starting material, but most of the detected product is the corresponding *N*-benzyl-1-phenylmethanimine. When toluene was used as solvent, traces of benzaldehyde were observed.

Next, we studied the scope of the nitrile reduction with the Fe(PNP^{Cy}) pincer complex **2** to illustrate the generality of this iron-catalyzed procedure. Therefore, various aromatic, aliphatic and heterocyclic nitriles (Table 2 and Scheme 3) were hydrogenated to their corresponding amines in high yields under mild conditions (30 bar H_2, 70–100 °C, 1 mol% **2**). Here, in general nitriles with electron withdrawing substituents such as halides or esters (Table 2, entries 2, 4 and 7) were hydrogenated in good yields. Only in the case of 3,5-difluorobenzonitrile no further increase of the yield was reached with 5 mol% catalyst loading (Table 2, entry 4). More interestingly, the hydrogenation of nitriles selectively took place even in the presence of an ester group producing an excellent yield (95%). 4-Phenyl substituted benzonitrile provided

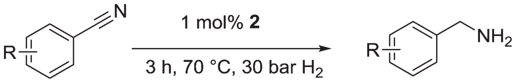
Table 1 Optimization of the reaction conditions for the hydrogenation of benzonitrile[a]

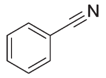
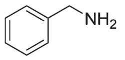
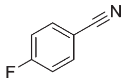
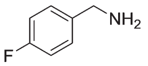
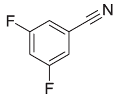
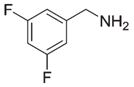
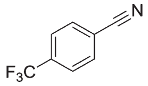
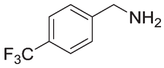
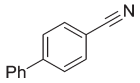
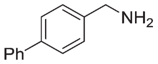
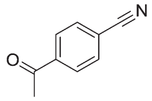
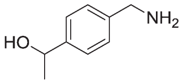
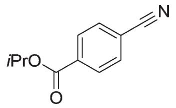
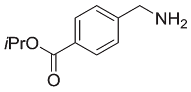
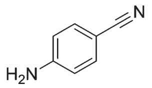
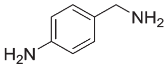
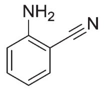
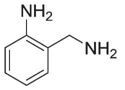
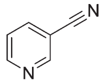
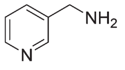
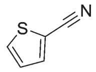
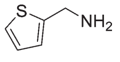


Entry	Catalyst [mol%]	Temp. [°C]	Time [h]	Conv.[b] [%]	Yield[b] [%]
1	0.5	70	3	99	90
2	1	70	3	99	89
3	1	70	2	99	86
4	1	55	3	92	—
5	1	40	3	44	—
6[c]	1	70	3	17	—

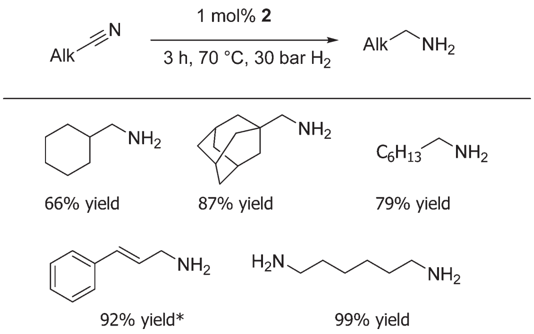
[a] Conditions: 1.0 mmol of benzonitrile, 1 mol% **2**, 2 mL of iPrOH, 30 bar H_2, 2–3 h, 40–70 °C. [b] Determined by GC analysis. [c] 2 mL of toluene.

Table 2 Hydrogenation of various (hetero)aromatic nitriles[a]



Entry	Nitrile	Amine	Yield[b] [%]
1[c]			95
2			84
3			41[d] 44[g]
4[d]			88
5			93
6[d]			63[f]
7[e]			95
8			70[f]
9			94 81[f]
10			41 84[g]
11[d]			90

[a] Conditions: 1.0 mmol of nitrile, 1 mol% **2**, 2 mL of iPrOH, 30 bar H_2, 3 h, 70 °C. [b] Determined by GC analysis. [c] 0.5 mol% **2**. [d] 30 bar H_2, 100 °C, 3 h. [e] 1 mol% **3**, 30 bar H_2, 100 °C, 3 h. [f] Isolated yields of ammonium salt. [g] 5 mol% **2**, 30 bar H_2, 100 °C, 3 h.



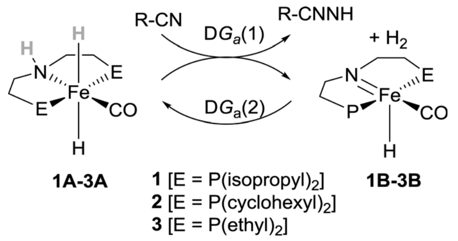
Scheme 3 Yield of different alkyl amines using **2**. Reaction conditions: 1.0 mmol of nitrile, 1 mol% **2**, 2 mL of iPrOH, 30 bar H_2, 3 h, 70 °C; * 100 °C, *ca.* 8% of C═C hydrogenation.

93% of the corresponding amine. Unfortunately, easily reducible ketone was not tolerated (Table 2, entry 6).

Regarding the influence of different substitutions in aminobenzonitrile, a higher yield was obtained for *ortho*-substituted derivatives (94%) compared to *para*-substituted ones (72%) (Table 2, entries 8 and 9). In addition, nitrogen- and sulfur-containing heteroaromatic nitriles (Table 2, entries 10 and 11) were hydrogenated to their corresponding amines with moderate to good yields up to 90%. No reaction was observed in the case of nitro- and hydroxyl-substituted benzonitriles, while 2-formylbenzonitrile was reduced to the corresponding alcohol.

Furthermore, the flexibility of Fe(PNP^{Cy}) pincer complex **2** as a suitable and selective homogeneous hydrogenation catalyst was demonstrated for the transformation of aliphatic nitriles and adipodinitrile to the corresponding amines (Scheme 3). Here, cyclic as well as linear nitriles are smoothly reduced in good yields under mild conditions (70 °C, 30 bar, 3 h) forming exclusively primary amines. In the case of cinnamyl nitrile, a higher temperature (100 °C) was needed in order to obtain full conversion. However, under these conditions small amounts of the C–C double bond were reduced. It should be pointed out that the synthesis of the industrially important hexane-1,6-diamine was performed with excellent selectivity and quantitative yield.

Finally, in order to understand the different reactivities of catalysts **1A–3A** (**1–3** without BH_3), B3PW91 density functional theory computations were carried out (see the ESI†). In our first study of the hydrogenation of nitrile to amine by using catalyst **1A**, an outer-sphere mechanism was identified based on experimental and computational analyses.[9] Here, the most important feature in this reaction is the reversible process between the hydrogenation and dehydrogenation of catalyst **1A** and its amido intermediate **1B**. In contrast to the first step from nitrile to imine, the second step from imine to amine is barrier less, while we compared only the difference in the first step for **1A–3A** (Scheme 4). For hydrogenation of acetonitrile, the free energy barrier is 17.55, 20.05 and 17.74 kcal mol^{-1} for catalysts **1A–3A**, respectively. The reaction is slightly exergonic for catalysts **1A** (−0.96 kcal mol^{-1}) and **3A** (−0.92 kcal mol^{-1}), but endergonic for catalyst **2A** (2.57 kcal mol^{-1}). Hence, for acetonitrile as an aliphatic nitrile, catalysts **1A** and **3A** have similar barriers, which are also close to those of catalyst regeneration; therefore catalysts **1A** and **3A** should have approximately the same reactivity. In contrast, catalyst **2A** has a higher barrier and should have lower reactivity, so that the regeneration of **2A** should determine the reaction rate. For benzonitrile as an aromatic nitrile, the free energy barrier is 15.35, 17.80 and 14.65 kcal mol^{-1} for catalysts **1A–3A**, respectively; the reaction is exergonic by 4.10, 0.56 and 4.05 kcal mol^{-1}, respectively. The computation for both cases shows that catalysts **1A** and **3A** should have similar reactivity, while the reactivity of catalyst **2A** should be lower. However, for the catalytic experiments a different sequence of reactivity was observed: Cy (**2**) = iPr (**1**) > Et (**3**). Comparing theory and



Scheme 4 Mechanism for nitrile hydrogenation and catalyst regeneration.

experiment reveals that the optimal conditions should be able to overcome the barrier of catalyst **2A** effectively. Obviously, the observed differences in reactivity among catalysts **1A–3A** are stronger influenced by the lower stability of catalyst **3A** then by kinetic effects. This assumption is supported by the vanished reactivity at low catalyst loading (Scheme 2).

In conclusion, the synthesis and application of the new iron PNP pincer complex **2** is presented. This catalyst allows for the selective hydrogenation of aromatic, aliphatic and heterocyclic nitriles including adipodinitrile to primary amines under mild conditions requiring no additive (base).

Acknowledgements

We thank B. Wendt, Dr. C. Fischer, S. Schareina and S. Buchholz (all at the LIKAT) for their excellent support. This work was supported by F. Hoffmann-La Roche Ltd.

Notes and references

‡ Catalytic procedure: catalytic transformations were performed in a 300 mL autoclave equipped with an internal aluminum plate to include seven uniform reaction glass vials (4 mL) sealed with cap, septum and needle. The autoclave was placed into an aluminum block as the heating system to perform the reactions. General procedure: in a reaction vial (4 mL), iron complex 2 (0.01 mmol) was mixed with 2 mL of iso-propanol (degassed). After a short time of stirring, the nitrile (1 mmol) was added under argon. The vial was placed into the alloy plate in the autoclave. The apparatus was purged three times with hydrogen, pressurized to 30 bar H_2, and stirred for 3 h at 70 or 100 °C. Afterwards, the autoclave was cooled to room temperature, depressurized, hexadecane was added as an internal standard and the reaction mixture was analysed by GC. Isolated HCl salts were analysed by NMR, GC-MS and HRMS.

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16 CCDC 1450524 data can be obtained free of charge from www.ccdc.cam.ac.uk/data_request/cif.