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Selective hydrogenation of nitriles to primary amines catalyzed by a novel iron complex†

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Hydrogenation of nitriles to primary amines constitutes an atom-efficient and environmentally benign synthetic reaction. Herein we present a novel complex based on earth-abundant iron, and its application in the catalytic homogeneous hydrogenation of (hetero)-aromatic, benzylic, and aliphatic nitriles to selectively form primary amines.

Catalytic hydrogenation of nitriles is of paramount industrial importance since the obtained amines and imines are versatile intermediates and precursors in the synthesis of various natural products, agrochemicals, pharmaceuticals, dyes, pigments and polymers.¹ Transition metal mediated hydrogenation of nitriles is usually accompanied by the formation of mixtures of primary amines, secondary amines and even tertiary amines *via* intermediate imine formation leading to crucial selectivity problem.² Of particular interest is the selective synthesis of primary amines,³ which is usually a difficult task owing to their high reactivity.

Today's synthetic chemistry focuses on cheaper, greener and atom-economic ways to carry out selective organic transformations.⁴ In this respect, the selective catalytic hydrogenation of nitriles represents an atom-economic, sustainable and environmentally benign route to valuable primary amines.

Conventionally, nitriles are reduced using stoichiometric amounts of metal hydrides, or hydrosilanes, which are effective but not environmentally benign, generating stoichiometric amounts of waste.^{5,6} On the other hand, heterogeneous catalysts based on Co, Ni and Pd, commonly used for nitrile hydrogenation in industry,^{7–9} often suffer from low selectivity towards primary amines and low functional group tolerance.

Homogeneous catalysts for the hydrogenation of nitriles are mostly limited to complexes of precious metals such as Ru, Rh, Ir, and Re.¹⁰ Economic constraints, limited availability, and toxicity issues of these platinum group metal catalysts have

promoted in recent years global research efforts towards the development of homogeneous catalysts based on earth-abundant, low-toxicity metal complexes.¹¹ Particularly attractive are complexes based on the first row metals Fe, Co, Ni and Mn.¹²

In fact, significant progress has been made in recent years in the development of catalysis with base-metal complexes for hydrogenation of various substrates, including olefins, alkynes, imines, N-heterocycles, CO₂, esters, ketones and aldehydes.^{13,14} However, hydrogenation of nitriles homogeneously catalysed by base-metal complexes has been scarcely investigated.¹⁵ To the best of our knowledge, there are only two reports on selective homogeneous hydrogenation of nitriles to primary amines using base-metal complexes, namely, catalysis by an aliphatic PNP-pincer based iron catalyst, reported by Beller,¹⁶ and by a PNNH-Co pincer catalyst recently reported by our group¹⁷ (Fig. 1).

Herein we report a novel iron complex bearing a dibenzylamine-type PNP ligand and no ancillary CO ligand, which is a pre-catalyst for selective hydrogenation of nitriles to primary amines.

Encouraged by the recent developments of catalysis by iron pincer complexes based on PNP ligands bearing aromatic or aliphatic backbones,^{12,13} we set out to design an iron complex based on a novel PNP pincer ligand in the pursuit of highly efficient iron catalysed nitrile hydrogenation to primary amines.

The new PNP ligand, bearing an N–H group, bis(2-diisopropylphosphinobenzyl)amine (**1**), which could form a flexible 6-membered chelate, while potentially exhibit hemilability, was prepared starting from bis(2-bromobenzyl)amine (see ESI†) (Scheme 1).

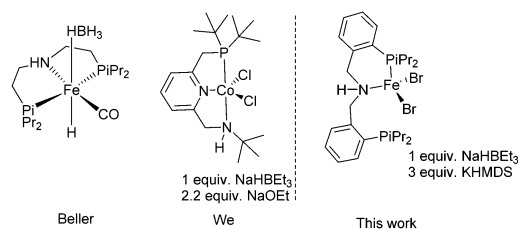
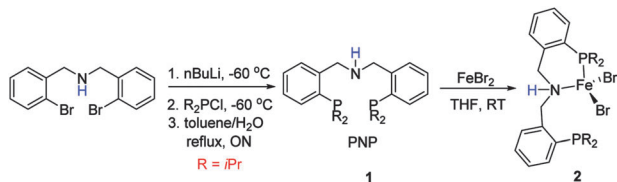


Fig. 1 Fe and Co based catalysts for homogeneous hydrogenation of nitriles to primary amines.

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† Electronic supplementary information (ESI) available: Experimental details, crystallographic information and spectral data. CCDC 1419077. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5cc08204h



Scheme 1 Synthetic access to PNP ligand (**1**) and the Fe(II)(PNP)Br₂ (**2**) complex.

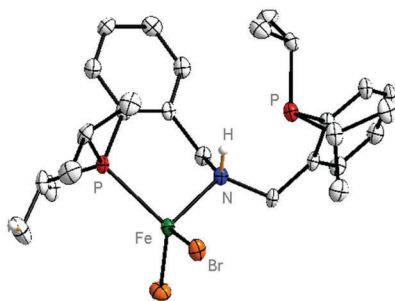


Fig. 2 Molecular structure of Fe(PNP)Br₂ (**2**) with thermal ellipsoids drawn at 50% probability level. All hydrogen atoms except for N–H are omitted for clarity.

The ligand was fully characterized by ¹H, ³¹P, ¹³CDEPT, COSY, HSQC and HMBC NMR experiments.

Treatment of the new PNP ligand with one equivalent of FeBr₂ at room temperature in THF led to the formation of the unsaturated, tetra-coordinated light green Fe(I)Br₂ complex (**2**) in 60% yield (Scheme 1). Complex **2** is a high spin paramagnetic complex and does not bind CO at room temperature.

Single crystals of complex **2** suitable for X-ray diffraction were obtained by slow diffusion of pentane into a saturated solution of toluene at room temperature after several days. A perspective view of the molecular structure of **2** is shown in Fig. 2.

Testing the activity of **2** as a pre-catalyst for the hydrogenation of nitriles, benzonitrile was used as a model substrate. We examined the influence of various amounts of additives, temperatures, hydrogen pressure and different solvents. Selected optimization experiments are shown in Table 1. First, the use of NaHBET₃ as a hydride source, and potassium hexamethyldisilazane (KHMDS) as a base were studied. Using NaHBET₃ (1 mol%), KHMDS (1 mol%) and complex **2** (1 mol%) at 60 bar H₂ and 140 °C in THF, only 19% of benzylamine were obtained after 16 h (Table 1, entry 1). Interestingly, increasing the amount of KHMDS to 2 mol% under the same conditions resulted in 73% of benzylamine (entry 2), and with 3 mol% of the base complete conversion of benzonitrile to selectively form benzylamine in 99% yield took place (Table 1, entry 3). In the absence of base, using 1 mol% NaHBET₃ and 1 mol% of **2**, no hydrogenation of benzonitrile took place (Table 1, entry 4) under similar reaction conditions. On the other hand, use of 3 mol% KHMDS in the absence of NaHBET₃ resulted in only 6% conversion (Table 1, entry 5). The catalytic activity depends strongly on the reaction temperature and pressure. At lower temperature (120 °C) and pressure (10 bar and 30 bar), the catalytic activity of **2** dropped significantly and lower yields of benzylamine

Table 1 Optimization of the reaction conditions for the hydrogenation of benzonitrile

Entry ^a	Solvent	NaHBET ₃ (mol%)	Base (mol%)	Time (h)	Conv. ^b (%)	Yield ^d (%)
1	THF	1	KHMDS (1)	16	19	19
2	THF	1	KHMDS (2)	16	73	73
3	THF	1	KHMDS (3)	16	99	99
4	THF	1	KHMDS (0)	16	0	0
5	THF	0	KHMDS (3)	16	6	6
6 ^c	THF	1	KHMDS (3)	16	9	9
7 ^d	THF	1	KHMDS (3)	16	39	39
8	THF	2	KHMDS (2)	16	43	43
9 ^e	THF	1	KHMDS (3)	16	32	29
10	THF	1	<i>t</i> BuOK (3)	16	74	62
11	THF	1	NaOMe (5)	16	70	67
12	THF	1	KH (3)	16	78	68
13	Dioxane	1	KHMDS (3)	16	99	99
14	Toluene	1	KHMDS (3)	16	99	96
15	<i>i</i> PrOH	1	KHMDS (3)	16	<2	<2
16	EtOH	1	KHMDS (3)	16	<1	<1
17	MeOH	1	KHMDS (3)	16	<1	<1
18 ^f	THF	1	KHMDS(3)	20	00	00

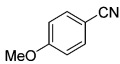

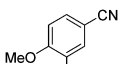







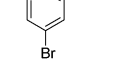



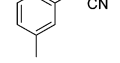





^a Conditions: benzonitrile (1 mmol), **2** (0.01 mmol), NaHBET₃, KHMDS and dry THF (2 mL), heated in an autoclave at 140 °C bath temperature.

^b Yields and conversions determined by GC-MS analysis using *m*-xylene as internal standard. ^c 10 bar H₂. ^d 30 bar H₂. ^e Reaction carried out at 120 °C. ^f The reaction was carried out without pre-catalyst **2**.

were obtained (Table 1, entries 6, 7 and 9) employing 1 mol% NaHBET₃, 3 mol% KHMDS and 1 mol% pre-catalyst **2** in THF. Exploring the effect of various bases, *t*BuOK, KH, and NaOMe were employed under similar reaction conditions, however lower yields of benzylamine (*t*BuOK, 62%; NaOMe, 67%; KH, 68%) resulted in comparison to when KHMDS was used (Table 1, entries 10–12). When dioxane or toluene were used as solvents, complete conversions of benzonitrile was observed but in the latter case, a small amount of secondary dibenzylimine (3%) was observed (Table 1, entries 13 and 14). However, using alcohols as solvents (EtOH, MeOH and *i*PrOH), only traces of hydrogenated benzylamine were observed (Table 1, entries 15–17) as revealed by GC-MS. A control experiment in the presence of 1 mol% NaHBET₃ and 3 mol% KHMDS but in the absence of pre-catalyst **2** did not result in any conversion of benzonitrile after 20 h under 60 bar H₂ at 140 °C in THF (Table 1, entry 18) and was recovered unchanged.

Using the optimized reaction conditions (THF, 140 °C, 60 bar H₂, 1 mol% NaHBET₃ and 3 mol% KHMDS), the generality of this iron-catalysed hydrogenation of nitriles was explored. As shown in Table 2, arenes with electron-donating substituents, including 4-methoxybenzonitrile, 2-methoxybenzonitrile, 3,4-dimethoxybenzonitrile, 4-methylbenzonitrile, and 3-methylbenzonitrile were hydrogenated to their corresponding primary amines 4-methoxybenzylamine, 2-methoxybenzylamine, 3,4-dimethoxybenzylamine, 4-methylbenzylamine, 3-methylbenzylamine in excellent yields (99%) (Table 2, entries 1–5). On the other hand, catalytic hydrogenation of benzonitriles substituted with the electron withdrawing F, Cl, and Br did not progress well

Table 2 Hydrogenation of various (hetero)aromatic, benzylic and aliphatic nitriles catalysed by complex **2**

Entry ^a	Substrate	Reaction conditions			
		Mol% (2)	Time (h)	Conv. ^b (%)	Yield ^b (%)
	$R-C\equiv N$	$\xrightarrow[\text{THF, 140 }^\circ\text{C, 60 bar H}_2]{\text{2 (1-5 mol\%)}, \text{NaEt}_3\text{BH (1-5 mol\%)}, \text{KHMDS (3-15 mol\%)}}$			
					$R-NH_2$
1		1	19	99	99
2		1	36	99	99
3		2	36	92	92
4		1	19	99	99
5		1	16	99	99
6		5	48	99	97
7		5	24	99	98
8		5	48	99	99
9		5	48	99	84
10		5	36	95	63
11		2	36	78	78
12		5	48	68	68
13		1	39	99	99
14		1	48	94	90
15		2	60	99	99
16		5	48	90	90
17		5	48	81	81
18 ^c		5	48	83	83
19		5	36	99	99
20 ^c		1	36	85	66

^a Conditions: nitrile (0.4–1 mmol), **2**/NaHBET₃/KHMDS ratio 1 : 1 : 3, H₂ (60 bar), and THF (2 mL), heated in an autoclave at 140 °C bath temperature. ^b Conversions and yields determined by GC-MS or ¹H NMR using *m*-xylene or toluene as internal standard. ^c The reactions were carried out using toluene as solvent.

under similar conditions, and the loadings of KHMDS, NaHBET₃ and the pre-catalyst had to be increased in order to obtain optimum yields and selectivity of corresponding primary amines. Thus, 4-fluoro- 3-fluoro, and 4-chloro benzonitriles furnished complete conversions, forming the corresponding substituted primary amines in 98%, 97% and 99% yields, respectively, when 5 mol% of **2** was employed in the presence of NaHBET₃ (5 mol%) and KHMDS (15 mol%) (Table 2, entries 6–8). 4-bromobenzonitrile produced 84% of 4-bromobenzylamine and 15% of secondary imine with a loading of 5 mol% catalyst (Table 2, entry 9). However, hydrogenation of 3-bromobenzonitrile gave 63% of 3-bromo-benzylamine and 32% of secondary imine under similar reaction conditions (Table 2, entry 10). 2-Naphthonitrile was hydrogenated to 2-naphthylmethylamine (78%) using 2 mol% pre-catalyst **2** after 36 h under 60 bar H₂ at 140 °C (Table 2, entry 11). To our delight, hydrogenation of the hetero-aromatic 3-pyridinecarbonitrile also furnished 3-picolylamine in 68% yield after 48 h of reaction time (Table 2, entry 12).

The potential of the catalyst was further probed by employing the more challenging and demanding benzylic and aliphatic nitriles bearing alpha hydrogen atoms. Benzyl cyanide, 3-methylbenzyl cyanide, 3,4-dimethoxybenzyl cyanide were hydrogenated to their corresponding 2-phenethylamine (99%), 3-methylphenethylamine (90%), 3,4-dimethoxyphenethylamine (99%), (Table 2, entries 13–15), respectively. Under the same reaction conditions hydrogenation of valerionitrile yielded pentylamine in 90% yield with 5 mol% pre-catalyst **2** and in the presence of NaHBET₃ and KHMDS (Table 2, entry 16). Hexanenitrile gave 81% hexylamine after 48 h under the loading of 5 mol% pre-catalyst **2** (Table 2, entry 17). Secondary alkyl nitriles, isobutyronitrile and cyclohexanenitrile were also hydrogenated to their corresponding isobutylamine (83%) and cyclohexylmethylamine (99%) in excellent yields with a loading of 5 mol% pre-catalyst **2** (Table 2, entries 18 and 19). However hydrogenation of crotonitrile gave 66% butylamine and 19% butyronitrile under the loading of 1 mol% precatalyst **2** in the presence of 1 mol% NaHBET₃ and 3 mol% KHMDS, indicating that the vinylic double bond does not remain intact (Table 2, entry 20).

Preliminary attempts were undertaken to isolate the catalytically active species. Reaction of **2** with 1 equiv. NaHBET₃, resulted in formation of a new paramagnetic complex along with a minute amount of free ligand **1**. However, we were unable to crystallize the obtained species, nor could we detect the often weak hydride stretching frequency by IR. Nevertheless, formation of a paramagnetic hydride complex of type Fe(1)(H)(Br) is possible, followed by its dehydrobromination by KHMDS, leading to a highly unsaturated species which may be stabilised by coordination of the second phosphine donor of the PNP ligand **1** and excess nitrile. In fact the possible coordination of the second phosphine donor was supported by an exemplary reaction of **2** with one equiv. of KHMDS under 1 atm CO giving a diphosphine dicarbonyl complex (see ESI†).

In conclusion, the preparation of a new PNP ligand **1** and of an iron complex based on it (**2**) is reported. This complex, in the presence of KHMDS and NaHBET₃ effectively catalyses the hydrogenation of nitriles. Various (hetero) aromatic, benzylic,

and aliphatic nitriles yield the corresponding primary amines selectively in good to excellent yields. Further investigations regarding the active species and the reaction mechanism are currently underway in our group.

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