Communication

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Selective Hydrogenation of Nitriles to Primary Amines Catalyzed by a Cobalt Pincer Complex

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Supporting Information Placeholder

ABSTRACT: The catalytic hydrogenation of nitriles to primary amines represents an atom-efficient and environmentally benign reduction methodology in organic chemistry. This has been accomplished in recent years mainly with precious-metal-based catalysts, with a single exception. Herein, the first homogeneous cobalt-catalyzed hydrogenation of nitriles to primary amines is reported. Several (hetero)aromatic-, benzylic- and aliphatic-nitriles undergo hydrogenation to the corresponding primary amines in good to excellent yields under the reaction conditions.

Amines constitute an important class of chemicals in industry. Most pharmaceuticals and agrichemicals contain amine groups and several amine intermediates are produced in bulk amounts[1], such as hexamethylene diamine, produced by heterogeneous hydrogenation of adiponitrile. Recent past witnessed several new catalytic methods for the synthesis of amines, such as amination of aryl halides with palladium,[2] hydroaminations[3] and hydroaminomethylation of olefins or alkynes,[4] homogeneous reductive aminations,[5] and the direct amination of alcohols[6]. Of particular interest is the selective synthesis of primary amines[6a,6c-6f]. Preparation of primary amines by reaction of ammonia with electrophiles is problematic, due to the higher nucleophilicity of the product primary amines as compared with ammonia. We[6a], and others[6c-6f] have reported the synthesis of primary amines directly from alcohols and ammonia. Another attractive route to primary amines is the hydrogenation of nitriles, due to the availability of starting materials, low price, and high atom efficiency. Traditionally, nitriles are reduced using stoichiometric amounts of metal hydrides,[7] hydrosilanes activated by a metal[8] or, organo-catalyst systems[9]. However, these methods suffer from poor atom efficiency, low functional group tolerance, laborious work-up, hazardous reagents and much waste production. Alternatively, the selective hydrogenation of nitriles represents a more economic and sustainable route to valuable primary amines in a ''green'' pathway.

The selective catalytic hydrogenation of nitriles to form primary amines is demanding. It often displays crucial selectivity problems, forming imines and a mixture of primary, secondary, and tertiary amines.[10] Hence, the choice of the catalyst and reaction conditions is imperative for obtaining high selectivity of the desired primary amines. Although heterogeneous catalytic systems for hydrogenation of nitriles, such as systems based on Co and Ni, are known[11], homogeneously catalyzed systems, which can be more selective and milder, involve complexes of precious metals,[12] except for a very recent report by Beller and co-workers using an iron pincer catalyst for hydrogenation of nitriles to primary amines[13]. Because of the higher cost, limited availability and often higher toxicity of noble metals, it is desirable to seek for homogeneous catalysts involving base-metals. Recent past witnessed noteworthy progress in the area of homogeneous earth abundant metal-based catalytic systems in hydrogenation reactions. Chirik and co-workers reported iron catalysts based on bis(imino)pyridine ligands, capable of the rapid hydrogenation of olefins at ambient temperatures and pressures.[14] Furthermore, we and other groups have also developed several iron-based catalysts for the hydrogenation of alkynes, ketones, aldehydes and esters.[14,15] Recently substantial efforts were made towards the development of cobalt catalysts for homogeneous hydrogenation reactions.[16] Chirik and co-workers developed diiminopyridine cobalt catalysts for olefin hydrogenation at room temperature [16c], and catalysts for asymmetric hydrogenation of sterically hindered alkenes[16e]. Hanson and co-workers reported an aliphatic PNP pincer catalyst for hydrogenation of aldehydes, ketones, imines, and alkenes, and dehydrogenation of secondary alcohols to ketones[16a,b]. Very recently, we have reported the first example of ester hydrogenation catalyzed by a pyridine-based PNN pincer cobalt complex[17]. However, homogeneously-catalyzed hydrogenation of nitriles by a cobalt complex has not been accomplished so far. We now report such a reaction, catalyzed by a cobalt PNNH pincer complex, yielding selectively primary amines.
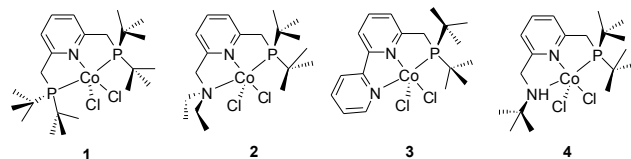
Figure 1. PNP- and PNN-based cobalt pincer complexes used in this study.

The hydrogenation reaction of benzonitrile to give benzylamine was chosen as a model system for this study. Thus, a dry benzene solution containing benzonitrile, a pincer Co complex (see Figure 1), NaEt₃BH, and KO*t*Bu were heated under 50 bar H₂ pressure at 135°C (bath temperature) for 36 h in an autoclave. The products were analyzed by GC–MS and NMR spectroscopy and identified by comparison with authentic samples. Hydrogenation of benzonitrile (1 mmol) with the pyridine-based PNP cobalt complex **1**[18] (4 mol%), NaEt₃BH (8 mol%) and KO*t*Bu (8.4 mol%) under 50 bar H₂ pressure at 135 °C in benzene (2 mL) resulted in 54% conversion after 36 h, yielding a mixture of benzylamine (41%) and *N*-benzylidene-1-phenylmethanamine (13%, Table 1, entry 1). However, when the reaction was carried out with the PNN complex **2**[17] (4 mol%), under the same conditions, 84% of benzylamine and 5% of *N*-benzylidene-1-phenylmethanamine were formed (Table 1, entry 2). Under similar reaction conditions, the bipyridyl-based PNN complex **3**[19] and 18% of dibenzylamine (Table 1, entry 3).

Table 1. Optimization of the reaction conditions for the hydrogenation of benzonitrile.[a]
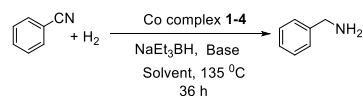
Entry	Co complex (mol%)	NaEt$_3$BH (mol%)	Base (mol%)	p(H$_2$) bar	Solvent	Conv. (%)[b]	Yield of benzylamine (%)[b]
1	**1** (4)	8	KO^{t}Bu (8.4)	50	benzene	54	41
2	**2** (4)	8	KO^{t}Bu (8.4)	50	benzene	89	84
3	**3** (4)	8	KO^{t}Bu (8.4)	50	benzene	83	65
4	**4** (4)	8	KO^{t}Bu (8.4)	50	benzene	96	96
5	**4** (4)	4	KO^{t}Bu (8.4)	50	benzene	97	97
6	**4** (3)	3	KO^{t}Bu (6.4)	50	benzene	88	86
7	**4** (2)	2	KO^{t}Bu (4.4)	50	benzene	85	85
8	**4** (1)	1	KO^{t}Bu (2.4)	50	benzene	72	69
9	**4** (2)	2	KO^{t}Bu (4.4)	50	toluene	89.5	80
10	**4** (2)	2	KO^{t}Bu (4.4)	50	THF	86	83
11	**4** (2)	2	KO^{t}Bu (4.4)	50	dioxane	87.5	86
12	**4** (2)	2	KH (4.4)	50	benzene	16.5	4
13	**4** (2)	2	NaOMe (4.4)	50	benzene	40.5	37
14	**4** (2)	2	KHMDS (4.4)	50	benzene	90	90
15	**4** (2)	2	NaOEt (4.4)	50	benzene	93.5	92
16	**4** (2)	2	NaOEt (4.4)	30	benzene	92	92
17	**4** (2)	2	NaOEt (4.4)	30	benzene	71	66[c]
18	**4** (2)	—	NaOEt (4.4)	30	benzene	88	66
19	**4** (2)	2	—	30	benzene	76	40
20	—	2	NaOEt (4.4)	30	benzene	—	—

[a] Reaction Conditions: benzonitrile (1 mmol), dry benzene (2 mL), performed in an autoclave at 135 °C (bath temperature); [b] Conversions and yields were determined by ^{1}H NMR spectroscopy with respect to toluene as an internal standard or by GC analysis; [c] reaction was carried out at 110 °C.

Interestingly, when the PNNH complex **4**[17] (4 mol%) was employed under analogous reaction conditions, the yield of the benzylamine increased to 96% with no side products being formed (Table 1, entry 4). Furthermore, lowering the NaEt$_3$BH loading from 8 mol% to 4 mol% resulted in a similar yield of benzylamine (97%) (Table 1, entry 5). When the same reaction was carried out in the presence of 3 mol% of complex **4**, 3 mol% NaEt$_3$BH, and 6.4 mol% KOtBu under 50 bar H$_2$ pressure at 135 °C in benzene (2 mL), benzylamine was formed in 86% yield (Table 1, entry 6). Lowering the cobalt complex loading to 2 mol% and 1 mol% resulted in 85% and 69% yield of benzylamine, respectively, after a reaction time of 36 h (Table 1, entries 7 and 8). Additionally, the effect of various solvents on the reaction was examined (Table 1, entries 7 and 9–11). A series of reactions was performed using 2 mol% of complex **4**, 2 mol% NaEt$_3$BH, and 4.4 mol% of KOtBu under 50 bar of H$_2$ pressure, and the yields were determined after 36 h. The use of toluene, 1,4-dioxane, and THF as solvents gave similar yields of benzylamine (80%, 83%, and 86%, respectively) with the formation of small amount of dibenzylamine in each case.

Next, the effect of different bases on the catalytic reaction was examined. While potassium bis(trimethylsilyl)amide (KHMDS),

KOtBu, and NaOEt were found to be suitable bases, the use of KH and NaOMe gave an unsatisfying yield of benzylamine (Table 1, entries 7 and 12–15). An increase in the yield of benzylamine was observed in the series KH (4%), NaOMe (37%), KOtBu (85%), KHMDS (90%), and NaOEt (92%). Gratifyingly, lowering of the H$_2$ pressure from 50 bar to 30 bar did not have an adverse effect on the reaction. Thus, when the reaction was carried out under 30 bar H$_2$ pressure using similar reaction conditions, benzylamine was selectively formed in 92% yield (Table 1, entry 16). However, upon decreasing the temperature the yield of benzylamine dropped to 66%, and 5% of N-benzylidene-1-phenylmethanamine was also formed (Table 1, entry 17). Interestingly, when the reaction was carried out in the absence of NaEt$_3$BH, benzylamine was formed in 66% together with dibenzylamine (22%). Eliminating NaOEt under analogous reaction conditions resulted in 40% yield of benzylamine and N-benzylidene-1-phenylmethanamine (36%) (Table 1, entry 19). In the absence of complex **4** under similar reaction conditions no conversion of benzylamine took place and benzonitrile was recovered unchanged (Table 1, entry 20).

Substrate scope of (hetero)aromatic nitriles: With the optimized reaction parameters in hand (Table 1, entry 16), we set out to test the generality of cobalt-catalysed hydrogenation of nitriles. Initially, various (hetero)aromatic nitriles were tested as substrates for the hydrogenation reaction. As shown in Table 2, (hetero)arenes with different substituents, both electron donating and electron withdrawing, were hydrogenated in good yields (Table 2, entries 1-15). Reaction of 4-methylbenzonitrile with 2 mol% of **4**, 2 mol% NaEt$_3$BH, and 4.4 mol% of NaOEt under 30 bar H$_2$ pressure at 135 °C in benzene (2 mL) produced exclusively 99% of 4-methylbenzylamine (Table 2, entry 1). Similarly, the catalytic reactions of 3-methylbenzonitrile under similar reaction conditions gave exclusively 99% of 3-methylbenzylamine (Table 2, entry 2). Further, the catalytic reaction of 4-methoxybenzonitrile and 2-methoxybenzonitrile under analogous reaction conditions yielded 99% of the corresponding benzylamines with 85% and 88% isolated yields of 4-methoxybenzylamine and 2-methoxybenzylamine, respectively (Table 2, entries 3 and 4). Moreover, 3,4-dimethoxybenzonitrile gave 99% conversion and 92% isolated yield of the corresponding 3,4-dimethoxybenzylamine (Table 2, entry 5). Under the standard reaction conditions hydrogenation of 4-fluorobenzonitrile, 3-fluorobenzonitrile, and 2-fluorobenzonitrile gave the corresponding benzylamine derivatives 4-fluorobenzylamine (83%), 3-fluorobenzylamine (78%), and 2-fluorobenzylamine (99%) in good yields (Table 2, entries 6-8). In case of 4-fluorobenzonitrile and 3-fluorobenzonitrile the corresponding dibenzylamine was formed in 10% and 9% yields, respectively (Table 2, entries 6 and 7). Notably, 4-chlorobenzonitrile gave 93% of 4-chlorobenzylamine and 4% of bis(4-chlorobenzyl)amine, with the halide substituent being tolerated (Table 2, entry 9). However, 4-bromobenzonitrile produced a mixture containing only 6% of 4-bromobenzylamine, 24% of N-(4-bromobenzylidene)-1-(4-bromophenyl)methaneamine, and < 1% of the corresponding secondary amine (Table 2, entry 10). 4-(trifluoromethyl)benzonitrile, 1-napthonitrile, and 4-aminobenzonitrile furnished 57% 4-(trifluoromethyl)benzylamine, 98% 1-napthylamine, and 86% 4-aminobenzylamine (Table 2, entries 11-13). In case of 4-(trifluoromethyl)benzonitrile and 4-aminobenzonitrile, formation of 41% and 9% of the corresponding secondary amines was observed. It seems that strongly electron withdrawing groups in the *para* position of the nitrile functionality have an adverse effect and furnish higher amounts of the secondary amines under the catalytic conditions,

Table 2. Hydrogenation of various (hetero)aromatic nitriles catalyzed by complex 4.

$$Ar \!-\!\!\equiv\!\!N + H_2 \text{ (30 bar)} \xrightarrow[\substack{\textbf{4} \text{ (2 mol\%)} \\ NaEt_3BH \text{ (2 mol\%)} \\ NaOEt \text{ (4.4 mol\%)} \\ Benzene, 135\,^0C \\ 36\text{ h}}]{} Ar\!\!\diagdown\!\!NH_2$$

Entry	Substrate	Product	Conv. (%)[b]	Yield (%)[b]
1			99	99
2			99	99
3			99	99(85)[c]
4			99	99(88)[c]
5			99	99(92)[c]
6			93	83
7			87	78
8			99	99
9			97	93
10			30	6
11			98	57
12			98	98
13			95	86
14			77	71
15			35	30

[a] Reaction Conditions: Nitrile (1mmol), **4** (2.0 mol%), NaEt₃BH (2 mol%), NaOEt (4.4 mol%), H₂ (30 bar) and benzene (2 mL) were heated in an autoclave at 135 ^{0}C (bath temperature); [b] Conversions and yields were determined by ^{1}H NMR spectroscopy with respect to toluene or dimethylformamide as an internal standard or by GC analysis; [c] Yield in the parantheses refers to the yield of the isolated product.

presumably by making the intermediate imine more susceptible to nucleophilic attack by the product primary amine. Interestingly, hetero-nitriles also underwent hydrogenation, albeit at a slower rate. Under analogous reaction conditions, 3-pyridinecarbonitrile and 6-methyl-2-pyridinecarbonitrile gave 71% of 3-picolylamine and 30% of 2-aminomethyl-6-methyl-pyridine, respectively (Table 2, entries 14 and 15). In case of both the hetero-aromatic nitriles, formation of 6% and 5% of the corresponding secondary amines was also observed.

Substrate scope of benzylic and aliphatic nitriles: Furthermore, the catalytic reaction was carried out with the more demanding nitriles bearing α hydrogens, furnishing the desired aliphatic primary amines in good to excellent yields under 30 bar H₂ pressure at 135°C using the pincer cobalt complex **4** (Table 3). Catalytic hydrogenations of aliphatic nitriles are much less investigated and are more challenging due to base-induced side

reactions when common hydrogenation catalysts are used. The study started with the hydrogenation of benzyl cyanide. Under the catalytic condition, it exclusively gave the corresponding 2-phenethylamine in 85% yield (Table 3, entry 1). Under analogous reaction conditions, 3-methylbenzyl cyanide, 3,4-dimethoxybenzyl cyanide, and 4-aminobenzyl cyanide yielded 99% of 3-methylphenethylamine, 86% of 3,4-dimethoxyphenethylamine, and 85% of 4-aminophenethylamine (Table 3, entries 2-4). Interestingly, 4-nitrobenzyl cyanide did not show any conversion under the present catalytic conditions (Table 3, entry 5). Even the nitro functionality remained intact in the substrate. The same effect of nitro-functionality was also observed by Beller and co-workers in iron catalyzed hydrogenation of nitriles[13]. Cyclohexanecarbonitrile furnished 90% cyclohexanemethylamine (Table 3, entry 6). Under the catalytic condition, butyronitrile produced 67% *n*-butylamine (Table 3, entry 7), valeronitrile gave 65% yield of the *n*-pentylamine and 5% of the corresponding secondary amine (Table 3, entry 8), while hexanenitrile yielded 65% *n*-hexylamine and 34% secondary amine (Table 3, entry 9).

Regarding the nature of the active cobalt catalyst, we believe that under the reaction conditions a double deprotonated monoanionic Co(I) complex is probably formed, by deprotonation of both the N–H and the methylene proton of the N-arm of the pincer ligand. Recently, we have isolated and crystallographically characterized a double deprotonated monoanionic ruthenium pincer complex based on a PNNH ligand[20]. The unique feature of the metal complexes developed with the PNNH ligand is that they have the potential for metal–ligand cooperation (MLC) by both amine–amide and aromatization–dearomatization ligand transformations, and hence are better capable of adopting to the requirements of the different steps of the catalytic cycle, providing a possible explanation as to why complex **4** is more effective than **2**. Recently, Chirik has shown that treatment of (PNP)CoCl₂ (**1**) with one equivalent, or two equivalents of NaHBEt₃ gave the Co(I) complexes (PNP)Co(I)Cl and (PNP)CoH, respectively[21]. Similarly, we also found that treatment of the complex (PNNH)CoCl₂ (**4**) with one equivalent of NaHBEt₃ at room temperature gave the paramagnetic (PNNH)Co(I)Cl, which was characterised by X-ray crystallography[17]. Although, we were not able to isolate the active catalyst in the nitrile hydrogenation reactions, we believe that *in-situ* a catalytically active monoanionic Co(I) hydride complex was formed by reaction with one equivalent of hydride source and two equivalents of base in the presence of H₂.

In conclusion, an unprecedented hydrogenation of nitriles to primary amines catalyzed by a cobalt complex is reported. Among the different cobalt complexes used herein, the PNNH-based cobalt pincer complex is the best pre-catalyst. The cobalt complex catalyzes the hydrogenation of various (hetero)aromatic nitriles, benzylic and aliphatic nitriles to the corresponding primary amines in good to excellent yields. The broad applicability of different functional groups and the relatively mild reaction conditions make this procedure interesting for the synthesis of different kinds of fine and bulk chemicals.

ASSOCIATED CONTENT

Supporting Information. Experimental details of the catalytic reactions and spectral details. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION
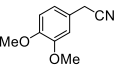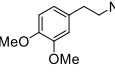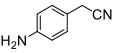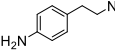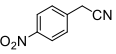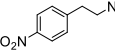
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Table 3. Hydrogenation of various benzylic and alphatic nitriles catalyzed by complex 4.

$$R\text{—}\equiv\text{N} + H_2 \text{ (30 bar)} \xrightarrow[\substack{NaEt_3BH\ (2\ mol\%)\\ NaOEt\ (4.4\ mol\%)\\ Benzene,\ 135\ ^0C\\ 60\ h}]{\textbf{4}\ (2\ mol\%)} R\text{—}\overset{\frown}{\ }NH_2$$

| Entry	Substrate	Product	Conv. (%)[b]	Yield (%)
1	benzyl cyanide	2-phenylethylamine	85	85
2	3-methylbenzyl cyanide	3-methylphenethylamine	99	99
3	MeO,OMe-benzyl cyanide	MeO,OMe-phenethylamine	86	86
4	H₂N-benzyl cyanide	H₂N-phenethylamine	85	85
5	O₂N-benzyl cyanide	O₂N-phenethylamine	-	-
6	cyclohexyl CN	cyclohexyl NH₂	90	90
7	propyl CN	propyl NH₂	67	67
8	pentyl CN	pentyl NH₂	70	65[c]
9	hexyl CN	hexyl NH₂	99	65[c]

[a] Reaction Conditions: Nitrile (1mmol), **4** (2.0 mol%), NaEt₃BH (2 mol%), NaOEt (4.4 mol%), H₂ (30 bar) and benzene (2 mL) were heated in an autoclave at 135 ^0C (bath temperature); [b] Conversions and yields were determined by ^1H NMR spectroscopy with respect to toluene or dimethylformamide or pyridine or mesitylene as an internal standard or by GC analysis;[c] formation of secondary amine was observed.

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ACKNOWLEDGMENT

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R—≡N → R⌒NH₂

Co complex, NaHBEt₃ / NaOEt, benzene / H₂ (30 bar), 135 °C

R = Aryl, Alkyl

24 examples
65-99%

Co complex