

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

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S Supporting Information

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. Here we report the first homogeneous Co-catalyzed hydrogenation of nitriles to primary amines. 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. The recent past has witnessed several new catalytic methods for the synthesis of amines, such as amination of aryl halides with Pd,² hydroaminations³ 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,c–f} 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–f} 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 These methods suffer from poor atom efficiency, low functional group tolerance, laborious workup, 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

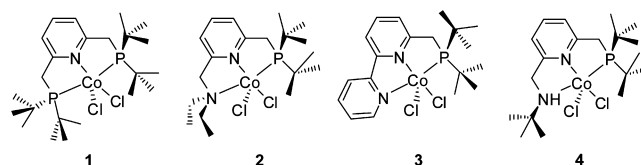


Figure 1. PNP- and PNN-based Co pincer complexes 1–4.

precious metals,¹² except for a very recent report by Beller et al. using an Fe 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 find homogeneous catalysts involving base metals. The recent past has witnessed noteworthy progress in the area of homogeneous earth-abundant metal-based catalytic systems in hydrogenation reactions. Chirik et al. reported Fe catalysts based on bis(imino)pyridine ligands, capable of the rapid hydrogenation of olefins at ambient temperatures and pressures.¹⁴ We and others have also developed several Fe-based catalysts for the hydrogenation of alkynes, ketones, aldehydes, and esters.^{14,15} Recently substantial efforts were made toward the development of Co catalysts for homogeneous hydrogenation reactions.¹⁶ Chirik et al. developed diiminopyridine Co catalysts for olefin hydrogenation at room temperature,^{16c} and catalysts for asymmetric hydrogenation of sterically hindered alkenes.^{16e} Hanson et al. 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 reported the first example of ester hydrogenation catalyzed by a pyridine-based PNNH pincer Co complex.¹⁷ However, homogeneously catalyzed hydrogenation of nitriles by a Co complex has not been accomplished so far. We now report such a reaction, catalyzed by a Co PNNH pincer complex, selectively yielding primary amines.

The hydrogenation 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 KOtBu was 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 Co complex **1**¹⁸ (4 mol%), NaEt₃BH (8 mol%), and KOtBu (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

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benzylamine (41%) and *N*-benzylidene-1-phenylmethanamine (13%, Table S1, entry 1). 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 S1, entry 2). Under similar reaction conditions, the bipyridyl-based PNN complex **3**¹⁹ (4 mol%) gave 65% of benzylamine and 18% of dibenzylamine (Table S1, entry 3) were obtained.

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 S1, entry 4). Furthermore, lowering the NaEt₃BH loading from 8 to 4 mol% resulted in a similar yield of benzylamine (97%) (Table S1, entry 5). When the same reaction was carried out in the presence of 3 mol% **4**, 3 mol% NaEt₃BH, and 6.4 mol% KOtBu under 50 bar H₂ pressure at 135 °C in benzene (2 mL), benzylamine was formed in 86% yield (Table S1, entry 6). Lowering the Co complex loading to 2 and 1 mol% resulted in 85% and 69% yield of benzylamine, respectively, after a reaction time of 36 h (Table S1, entries 7, 8). Additionally, the effects of various solvents on the reaction were examined (Table S1, entries 7, 9–11). A series of reactions was performed using 2 mol% **4**, 2 mol% NaEt₃BH, and 4.4 mol% KOtBu under 50 bar H₂ 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 a 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 S1, entries 7, 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 H₂ pressure from 50 to 30 bar did not have an adverse effect on the reaction. Thus, when the reaction was carried out under 30 bar H₂ pressure using similar reaction conditions, benzylamine was selectively formed in 92% yield (Table S1, entry 16). Upon decreasing the temperature, the yield of benzylamine dropped to 66%, and 5% of *N*-benzylidene-1-phenylmethanamine was also formed (Table S1, entry 17). Interestingly, when the reaction was carried out in the absence of NaEt₃BH, benzylamine was formed in 66% yield, together with dibenzylamine (22%). Eliminating NaOEt under analogous reaction conditions resulted in 40% yield of benzylamine and *N*-benzylidene-1-phenylmethanamine (36%) (Table S1, entry 19). In the absence of complex **4** under similar reaction conditions, no conversion of benzylamine took place, and benzonitrile was recovered unchanged (Table S1, entry 20).

Substrate Scope of (Hetero)aromatic Nitriles. With the optimized reaction parameters in hand (Table S1, entry 16), we set out to test the generality of Co-catalyzed hydrogenation of nitriles. Initially, various (hetero)aromatic nitriles were tested as substrates for the hydrogenation reaction. As shown in Table 1, (hetero)arenes with different substituents, both electron-donating and electron-withdrawing, were hydrogenated in good yields. Reaction of 4-methylbenzonitrile with 2 mol% **4**, 2 mol% NaEt₃BH, and 4.4 mol% NaOEt under 30 bar H₂ pressure at 135 °C in benzene (2 mL) produced exclusively 99% of 4-methylbenzylamine (Table 1, entry 1). Similarly, the catalytic reactions of 3-methylbenzonitrile under similar reaction conditions gave exclusively 99% of 3-methylbenzylamine (Table 1, entry 2). Further, the catalytic reaction of 4-

Table 1. Hydrogenation of Various (Hetero)aromatic Nitriles Catalyzed by **4**

$$\text{Ar}-\text{C}\equiv\text{N} + \text{H}_2 \text{ (30 bar)} \xrightarrow[\text{NaEt}_3\text{BH (2 mol\%)}]{\text{4 (2 mol\%)}} \text{Ar}-\text{CH}_2\text{NH}_2$$

NaOEt (4.4 mol%)
 Benzene, 135 °C, 36 h

| 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 |

^aConditions: nitrile (1 mmol), **4** (2.0 mol%), NaEt₃BH (2 mol%), NaOEt (4.4 mol%), H₂ (30 bar), and benzene (2 mL), heated in an autoclave at 135 °C bath temperature. ^bConversions and yields determined by ¹H NMR spectroscopy with respect to toluene or dimethylformamide as an internal standard or by GC analysis. ^cYields in parentheses refer to isolated product.

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 1, entries 3, 4). Moreover, 3,4-dimethoxybenzonitrile gave 99% conversion and 92% isolated yield of the corresponding 3,4-dimethoxybenzylamine (Table 1, entry 5). Under the standard reaction conditions, hydrogenation of 4-fluorobenzonitrile, 3-fluorobenzonitrile, and 2-fluorobenzonitrile gave the corre-

sponding benzylamine derivatives 4-fluorobenzylamine (83%), 3-fluorobenzylamine (78%), and 2-fluorobenzylamine (99%) in good yields (Table 1, entries 6–8). In the cases of 4-fluorobenzonitrile and 3-fluorobenzonitrile, the corresponding dibenzylamine was formed in 10% and 9% yields, respectively (Table 1, entries 6, 7). Notably, 4-chlorobenzonitrile gave 93% of 4-chlorobenzylamine and 4% of bis(4-chlorobenzyl)amine, with the halide substituent being tolerated (Table 1, entry 9). However, 4-bromobenzonitrile produced a mixture containing only 6% of 4-bromobenzylamine, 24% of *N*-(4-bromobenzylidene)-1-(4-bromophenyl)methanamine, and <1% of the corresponding secondary amine (Table 1, entry 10). 4-(Trifluoromethyl)benzonitrile, 1-naphthonitrile, and 4-aminobenzonitrile furnished 57% 4-(trifluoromethyl)benzylamine, 98% 1-naphthylamine, and 86% 4-aminobenzylamine (Table 1, entries 11–13). In the cases 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, presumably by making the intermediate imine more susceptible to nucleophilic attack by the product primary amine. Interestingly, heteronitriles also underwent hydrogenation, albeit at a slower rate. Under analogous reaction conditions, 3-pyridinecarbonitrile and 6-methyl-2-pyridinecarbonitrile gave 71% of 3-picolyamine and 30% of 2-aminomethyl-6-methylpyridine, respectively (Table 1, entries 14, 15). In the cases of both heteroaromatic 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 -H's, furnishing the desired aliphatic primary amines in good to excellent yields under 30 bar H_2 pressure at 135 °C using the pincer Co complex **4** (Table 2). 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 conditions, it exclusively gave the corresponding 2-phenethylamine in 85% yield (Table 2, 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 2, entries 2–4). Interestingly, 4-nitrobenzyl cyanide did not show any conversion under the present catalytic conditions (Table 2, entry 5). Even the nitro functionality remained intact in the substrate. The same effect of nitro functionality was also observed by Beller et al. in Fe-catalyzed hydrogenation of nitriles.¹³ Cyclohexanecarbonitrile furnished 90% cyclohexanemethylamine (Table 2, entry 6). Under the catalytic conditions, butyronitrile produced 67% *n*-butylamine (Table 2, entry 7), valeronitrile gave 65% yield of the *n*-pentylamine and 5% of the corresponding secondary amine (Table 2, entry 8), and hexanenitrile yielded 65% *n*-hexylamine and 34% secondary amine (Table 2, entry 9).

Regarding the nature of the active Co 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 isolated and crystallographically characterized a double-deprotonated monoanionic ruthenium

Table 2. Hydrogenation of Various Benzylic and Aliphatic Nitriles Catalyzed by **4**

| | | $R-C\equiv N + H_2 \text{ (30 bar)} \xrightarrow[\text{NaOEt (4.4 mol\%)}]{\text{4 (2 mol\%)}} R-CH_2NH_2$ NaEt ₃ BH (2 mol%) Benzene, 135 °C, 60 h | | |
|-------|-----------|---|------------------------|-----------------|
| Entry | Substrate | Product | Conv. (%) ^b | Yield (%) |
| 1 | | | 85 | 85 |
| 2 | | | 99 | 99 |
| 3 | | | 86 | 86 |
| 4 | | | 85 | 85 |
| 5 | | | - | - |
| 6 | | | 90 | 90 |
| 7 | | | 67 | 67 |
| 8 | | | 70 | 65 ^c |
| 9 | | | 99 | 65 ^c |

^aConditions: nitrile (1 mmol), **4** (2.0 mol%), NaEt₃BH (2 mol%), NaOEt (4.4 mol%), H_2 (30 bar), and benzene (2 mL), heated in an autoclave at 135 °C bath temperature. ^bConversions and yields determined by ¹H NMR spectroscopy with respect to toluene, dimethylformamide, pyridine, or mesitylene as an internal standard or by GC analysis. ^cFormation of secondary amine was observed.

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 by both amine–amide and aromatization–dearomatization ligand transformations, and hence are better capable of adapting to the requirements of the different steps of the catalytic cycle, providing a possible explanation as to why **4** is more effective than **2**. Recently, Chirik showed that treatment of (PNP)CoCl₂ (**1**) with 1 and 2 equiv 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 1 equiv of NaHBET₃ at room temperature gave the paramagnetic (PNNH)Co(I)Cl, which was characterized 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 1 equiv of hydride source and 2 equiv of base in the presence of H_2 .

In conclusion, an unprecedented hydrogenation of nitriles to primary amines homogeneously catalyzed by a Co complex is reported. Among the different Co complexes used herein, the PNNH-based Co pincer complex is the best precatalyst. The Co complex catalyzes the hydrogenation of various (hetero)-aromatic, 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. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.Sb04879.

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