Old Concepts, New Application – Additive-Free Hydrogenation of Nitriles Catalyzed by an Air Stable Alkyl Mn(I) Complex

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Abstract: An efficient additive-free manganese-catalyzed hydrogenation of nitriles to primary amines with molecular hydrogen is described. The pre-catalyst, a well-defined bench-stable alkyl bisphosphine Mn(I) complex \( \text{fac-}[\text{Mn(dpre})(\text{CO})_3(CH_3)] \) (dpre = 1,2-bis(di-n-propylphosphino)ethane), undergoes CO migratory insertion into the manganese-alkyl bond to form acyl complexes which upon hydrogenolysis yields the active coordinatively unsaturated Mn(I) hydride catalyst \([\text{Mn(dpre)}(\text{CO})_2(H)]\). A range of aromatic and aliphatic nitriles were efficiently and selectively converted into primary amines in good to excellent yields. The hydrogenation of nitriles proceeds at 100 °C with a catalyst loading of 2 mol% and a hydrogen pressure of 50 bar. Mechanistic insights are provided by means of DFT calculations.

Keywords: manganese; alkyl complexes; hydrogenation; nitriles; migratory insertion

Introduction

Amines constitute an important class of organic compounds which are used as versatile building blocks for the bulk and fine chemical industries.[1] A very attractive, atom-economic, and sustainable route to obtain selectively primary amines is the hydrogenation of nitriles with molecular hydrogen utilizing well-defined catalysts based on Earth abundant non-pre-cious metals.[2–4] In particular base metals such as iron and manganese are promising candidates as these belong to the most abundant metals in the Earth crust, are inexpensive, and exhibit a low environmental impact. While iron, cobalt, and nickel catalysts for the hydrogenation of polar multiple bonds such as carbonyl compounds, imines, and nitriles had been subject of intense investigation over the past decade,[5–11] low valent Mn(I) catalysts just appeared in 2016 as new but very powerful players in this fast growing area.[6–11] As hydrogenation of nitriles is concerned, several well-defined catalysts based on iron,[12] cobalt[13] and lately also manganese (Scheme 1)[14] have been described.[15] It is interesting to note that most of these reactions require additives (strong base) in order to activate the pre-catalysts.

In this article, we report on the synthesis and application of a bench-stable and well-defined alkyl bisphoshine Mn(I) complex as efficient pre-catalyst for the selective hydrogenation of nitriles to give primary amines. It has to be noted that this is the first example of a manganese-catalyzed hydrogenation of nitriles without the need of an additive (base) utilizing a well-defined Mn(I) complex. The activation of the pre-catalyst takes advantage of the fact that (i) CO ligands of Mn(I) alkyl carbonyl complexes are able to undergo migratory insertions to form acyl complexes in the presence of strong field ligands such as CO or tertiary phosphines – a well-known textbook reaction.[16] and that (ii) heterolytic cleavage of molecular hydrogen by acyl complexes affords aldehydes and coordinatively unsaturated metal hydride intermediates – a key step in both stoichiometric and catalytic hydroformylations of alkenes.[17] Thus, the catalytic hydrogenation of nitriles is initiated by migratory insertion of a CO ligand into...
the Mn-alkyl bond to yield acyl intermediates which undergo rapid hydrogenolysis to form the active 16e− Mn(I) hydride catalysts as shown in Scheme 2.

**Results and Discussion**

In addition to the known Mn(I) complexes [Mn(CO)₅(CH₃)] (1)¹⁸,¹⁹, fac-[Mn(bipy)(CO)₃(CH₃)] (2)²⁰, the new Mn(I) complexes fac-[Mn(dpre)(CO)₃(H)] (dpre = 1,2-bis(di-n-propyl-phosphino)ethane) (4) and fac-[Mn(dpre)(CO)₃(CH₃)] (5)²¹ were synthesized, characterized, and applied. The hydride complex fac-[Mn(dpre)(CO)₃(H)] (4) was obtained by reacting a suspension of [Mn₂(CO)₁₀] and 1,2-bis(dipropylphosphino)ethane in anhydrous n-pentanol at 140°C for 5 h in low yield (14%). The neutral methyl Mn(I) complex 5 was obtained by reacting fac-[Mn(dpre)(CO)₃(Br)] (3) with NaK and subsequently with CH₃I in 64% isolated yield (Scheme 3). The resulting off-white complex was fully characterized by ¹H, ¹³C, ¹⁹F, and ³¹P NMR and IR spectroscopy, and high-resolution mass spectrometry. The IR spectrum contains strong CO stretching vibrations at 1974, 1888 and 1835 cm⁻¹ which clearly indicate the coordination of three CO ligands to the metal center in a facial arrangement. In the ¹H and ¹³C NMR spectra the methyl group gives rise to triplet resonances at −0.70 (J = 9.0 Hz) and −16.8 ppm (J = 18.2 Hz), respectively.

The catalytic performance of complexes 1, 2, 4, and 5 (Scheme 4) was then investigated for the hydrogenation of 4-fluorobenzonitrile as model substrate. Selected optimization experiments are depicted in Table 1. With a catalyst loading of 3 mol% at 100°C and a hydrogen pressure of 50 bar H₂ in toluene for

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*Scheme 1. Manganese Catalysts for the Hydrogenation of Nitriles.*

*Scheme 2. Formation of an Unsaturated Mn(I) Hydride Species via Alkyl Migration and Hydrogenolysis of an Acyl Intermediate.*

*Scheme 3. Synthesis of fac-[Mn(dpre)(CO)₃(CH₃)] (5).*
18 h no reaction took place with complexes 1, 2 and 4 as pre-catalysts. This clearly emphasizes that strongly electron donating co-ligands such as alkyl bisphosphines are required to achieve high catalytic activity. Moreover, the coordinatively saturated and inert hydride complex 4 is inactive due to the lack of a vacant coordination site. Accordingly, complex 4 is not an intermediate in the catalytic process which is obviously a metal-centered, i.e., an inner-sphere, reaction. Under the same reaction conditions with complex 5 but a catalyst loading of 2 mol%, 4-fluorobenzylamine was obtained in 95% yield (Table 1, entry 4). Similar results were obtained with 5 in iPrOH (Table 1, entry 5), whereas no reaction took place in this solvent in the absence of H₂ thus clearly excluding a transfer hydrogenation process (Table 1, entry 6). At lower temperature (80 °C) or a lower catalyst loading (1 mol%), the catalytic activity dropped significantly and no or lower conversions of 4-fluorobenzonitrile were achieved (Table 1, entries 7 and 8).

Having established the best reaction conditions, the applicability of catalyst 5 is demonstrated in the selective hydrogenation of various nitriles, including substituted aromatic, benzylic, aliphatic nitriles and dinitriles. The results for aromatic substrates are shown in Tables 2 and 3. Substrates with electron-withdrawing substituents such as halides containing substrate are very efficiently converted to amines in excellent yields (Table 2, entries 1–5). Good yields are achieved for substrates with electron-donating substituents such as methyl, methoxy and amino groups (Table 2, entries 7–9). Heterocycles, for instance, pyridine and thiophene derivatives are well tolerated (Table 2, entries 10–12).

No reaction was observed in the case of 2-(4-nitrophenyl)acetonitrile (Table 3, entry 1) indicating catalyst deactivation. Dinitriles were reduced to the corresponding diamines in good to excellent yields (Table 3, entries 4–6). Interestingly, aliphatic dinitriles, such as adiponitrile (Table 3, entry 5) gave higher yields in comparison to the aromatic analogues (Table 3, entry 4). Finally, linear aliphatic nitriles were reduced to the corresponding amines in excellent yields (Table 3, entries 7–11).

A reasonable mechanism for the hydrogenation of nitriles was established by means of DFT calculations in toluene with benzonitrile as model substrate. The initiation step and the key intermediates along the

### Table 1. Optimization of the Reaction Conditions for the Hydrogenation of 4-Fluorobenzonitrile

| entry | catalyst | X (mol%) | solvent | T (°C) | conversion (%) | yield (%) |
|-------|----------|----------|---------|--------|---------------|----------|
| 1     | [Mn(CO)₃(CH₃)] (1) | 3        | toluene | 100    | –             | –        |
| 2     | fac-[Mn(bipy)(CO)₃(CH₃)] (2) | 3        | toluene | 100    | –             | –        |
| 3     | fac-[Mn(dpre)(CO)₃(H)] (4) | 3        | toluene | 100    | –             | –        |
| 4     | fac-[Mn(dpre)(CO)₃(CH₃)] (5) | 2        | toluene | 100    | >99           | 95       |
| 5     | fac-[Mn(dpre)(CO)₃(CH₃)] (5) | 2        | iPrOH   | 100    | >99           | 93       |
| 6     | fac-[Mn(dpre)(CO)₃(CH₃)] (5) | 2        | iPrOH   | 100    | –             | –        |
| 7     | fac-[Mn(dpre)(CO)₃(CH₃)] (5) | 1        | toluene | 100    | 37            | 11       |
| 8     | fac-[Mn(dpre)(CO)₃(CH₃)] (5) | 2        | toluene | 80     | –             | –        |

[a] Reaction conditions: 4-Fluorobenzonitrile (0.6 mmol), 50 bar H₂, 5 mL solvent, 18 h.
[b] Conversion determined by ¹⁹F{¹H} NMR analysis.
[c] Yield determined by ¹⁹F{¹H} NMR analysis using fluorobenzene as standard.
[d] In the absence of H₂.
catalytic cycle are presented in Figures 1 and 2 (see supporting information for details). The active species is formed by methyl migration to a CO ligand in complex 5 (A in the calculations, Figure 1) producing...
acyl complex B which is stabilized by a C–H agostic interaction. This step is endergonic (ΔG = 10.8 kcal/mol) with an accessible barrier of 12.0 kcal/mol. Upon addition of H₂, the dihydrogen complex D is formed. This step has a barrier of 9.0 kcal/mol and is slightly endergonic (ΔG = 3.3 kcal/mol). Protonation of the acyl ligand through H-transfer from the dihydrogen ligand takes place yielding finally intermediate E, featuring a hydride ligand and an O-coordinated acetaldehyde. The last step, from D to E, goes over a 5.4 kcal/mol barrier and has a favorable free energy balance of ΔG = −2.1 kcal/mol. The highest barrier along the initiation process is 18.1 kcal/mol corresponding to the energy of transition state TS_CD.

A simplified catalytic cycle is depicted in Figure 2. The reaction begins with exchange of the aldehyde in intermediate E by one molecule of nitrile to form F, the initial species in the cycle with an N-coordinated benzonitrile. From here the reaction consists of two consecutive H₂ additions to the substrate going from a nitrile to an amine group. The catalytic cycle starts with hydride transfer to the C-atom of the nitrile group producing an intermediate with a side-bonded C=N double bond that is further stabilized by a C–H agostic interaction (G). This is an endergonic step (ΔG = 7.0 kcal/mol) with a moderate barrier of 8.2 kcal/mol. A ligand rearrangement from side to end on coordination leads to intermediate H. Here, the PhCHC=N ligand is coordinated by the N-atom becoming a 4-electron donor and establishing a Mn=N double bond as indicated by a short Mn–N distance (1.76 Å) and a Mn–N–C angle of 173° approaching linearity. The free energy balance for this rearrangement is very favorable: ΔG = −19.0 kcal/mol. The path proceeds with H₂ coordination reaching intermediate K, a dihydrogen species. Overall, the coordination of dihydrogen overcomes a significant barrier of 21.6 kcal/mol, being also unfavorable, from the thermodynamic point of view, K being 19.9 kcal/mol less stable than H. The reaction continues with N-protonation via H-transfer from the dihydrogen ligand. This leads to intermediate M presenting an N-coordinated imine ligand, with a barrier of 6.9 kcal/mol and a favorable free energy balance of ΔG = −20.1 kcal/mol. This concludes the first part of the mechanism, where one equivalent of H₂ was added to the initial benzonitrile forming the corresponding imine PhCH=NH.

The second part of the catalytic cycle starts with a rearrangement of the coordination mode of the imine ligand in M, followed by hydride transfer to the imine C-atom resulting in intermediate P containing a N-coordinated amido ligand. The overall process has a barrier of 14.1 kcal/mol and is favorable by −6.9 kcal/mol. The mechanism proceeds with coordination of the second H₂ molecule resulting in the dihydrogen complex R which features an amido co-ligand. Coordination of the second dihydrogen molecule is equivalent to what was found for the first one with similar barrier and free energy balance (21.2 kcal/mol).

The final step along the path corresponds to protonation of the N-atom in R, in a facile step with a negligible barrier of 2.0 kcal/mol and a very favorable free energy balance (ΔG = −27.5 kcal/mol). In the final intermediate, S, the reaction product (benzylamine) is already formed and remains N-coordinated to the metal. From S, ligand exchange with loss of the product and addition of a new nitrile molecule closes the cycle and regenerates the starting intermediate F with a neutral free energy balance of ΔG = 0 kcal/mol. The overall reaction barrier is 26.8 kcal/mol, measured from H to the transition state of N-protonation (TSKL, see supporting information). This is a high barrier that...
may be slightly overestimated but reflects the reaction conditions (18 h at 100°C).

**Conclusion**

In sum, we report an efficient hydrogenation of nitriles with molecular hydrogen catalyzed by a well-defined, bench-stable bisphosphine Mn(I) complex. Our results indicate that an inner-sphere (metal-centered) process without ligand participation is taking place. To the best of our knowledge, this is the first example of an additive-free hydrogenation of nitriles catalyzed by a well-defined Mn(I) complex. These reactions are atom economic implementing an inexpensive, earth abundant non-precious metal catalyst. The catalytic process is initiated by migratory insertion of a CO ligand into the Mn-alkyl bond to yield an acyl intermediate which undergoes rapid hydrogenolysis to form the active 16e^– Mn(I) hydride catalyst [Mn(dppe)(CO)\(_2\)(H)] – a conceptually new approach in Mn(I) hydrogenation chemistry. A range of (hetero)aromatic and aliphatic nitriles were efficiently converted into primary amines, respectively, in good to excellent isolated yields. The hydrogenation of nitriles proceeds at 100°C with a catalyst loading of 2 mol %. A hydrogen pressure of 50 bar was applied and the reaction time was 18 h. The mechanism obtained by means of DFT calculations consists of two successive and equivalent H\(_2\) additions to the initial nitrile substrate. The crucial features in the path are hydride transfer to the substrate C-atom,
followed by protonation of the corresponding N-atom, deriving from key hydride and dihydrogen intermediates, respectively.

**Experimental Section**

**General Information.** All reactions were performed under an inert atmosphere of argon by using Schlenk techniques or in an MBraun inert-gas glovebox. The solvents were purified according to standard procedures. The deuterated solvents were purchased from Aldrich and dried over 3 Å molecular sieves.

**General Procedure for the Hydrogenation of Nitriles.** Inside an Ar-flushed glovebox, the nitrile (0.6 mmol, 1 equiv.) and fac-[Mn(dpre)(CO)](H)(CH₃)] (5) (0.006–0.022 mmol, 0.01–0.04 equiv.) were mixed with 5 mL of the anhydrous solvent and transferred into a steel autoclave, which was three times evacuated and flushed with Ar prior use. The autoclave was flushed three times with hydrogen, 50 bar H₂ pressure were applied and the autoclave was placed in an oil bath (80–100 °C) and the reaction was run for 18 h. The autoclave was then cooled in an ice bath for 10 min. The reaction mixture was filtrated through a PTFE membrane and analyzed by 

**Isolation of Product as Ammonium Salt.** The reaction mixture was filtrated through a short plug of Celite and diluted with Et₂O to 25 mL and 1 M HCl in Et₂O was added drop wise until precipitation was complete. The solution was decanted and the ammonium salt was several times washed with Et₂O and dried under vacuum.

**Computational Details.** The computational results presented have been achieved in part using the Vienna Scientific Cluster (VSC). All calculations were performed using the Gaussian 09 software without symmetry constraints. The optimized geometries were obtained with the the PBE0 functional. That functional uses a hybrid generalized gradient approximation (GGA), including 25% mixture of Hartree-Fock metries were obtained with the the PBE0 functional. That functional uses a hybrid generalized gradient approximation (GGA), including 25% mixture of Hartree-Fock

**Identification of Intermediates.** The electronic energies (basis b1) consisted of the Stuttgart/Dresden ECP (SDD) basis set to describe the electrons of manganese, and a standard 6-31G(d,p) basis set for all other atoms. Transition state optimizations were performed with the Synchronous Transit-Guided Quasi-Newton Method (STQNM) developed by Schlegel et al. following extensive searches of the Potential Energy Surface. Frequency calculations were performed to confirm the nature of the stationary points, yielding one imaginary frequency for the transition states and none for the minima. Each transition state was further confirmed by following its vibrational mode downhill on both sides and obtaining the minima presented on the energy profiles. The electronic energies (Eₑ) obtained at the PBE0/b1 level of theory were converted to free energy at 298.15 K and 1 atm
(G_3) by using zero point energy and thermal energy corrections based on structural and vibration frequency data calculated at the same level. The free energy values presented were corrected for dispersion by means of Grimme DFT–D3 method\textsuperscript{[33]} with Becke and Johnson short distance damping.\textsuperscript{[34]} Solvent effects (toluene) were considered in all calculations using the Polarizable Continuum Model (PCM) initially devised by Tomasi and coworkers\textsuperscript{[35]} with radii and non-electrostatic terms of the SMD solvation model, developed by Truhlar et al.\textsuperscript{[36]}

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