Phosphoric Acid Bridged Cobalt Bis(dicarbollide) Ion as a Highly Efficient Catalyst for the Organocatalytic Hydrogenation of Ketimines

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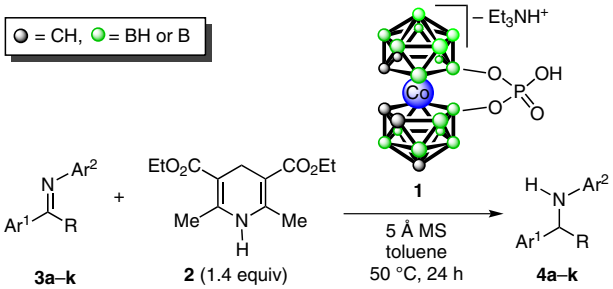
Abstract: The high-yield reduction of aromatic ketimines into amines by using a novel catalyst based on a metallacarborane structure, 8,8′-μ-phosphate[(1,2-dicarba-*closo*-undecaborane)-3,3′-cobalt(-1)(1′,2′-dicarba-*closo*-undecaborane)] acid, is described.

Key words: metallacarboranes, hydrogenation, catalysis, reduction, imines, amines

Amines are important structural elements in biologically active natural products and pharmaceuticals.[1] Imine reduction is a widespread approach to the preparation of amines, and a range of methods for reducing imines have been reported, including metal-catalyzed hydrogenation[2] and hydrosilylation.[3] Transfer hydrogenation of imines by using a hydrogen donor in combination with an acid catalyst has recently emerged as an efficient method for the preparation of amines. In particular, the Hantzsch ester is recognized as an effective and useful hydrogen donor.[4] Several acid catalysts, including thiourea derivatives[5] and molecular iodine,[6] have been used to reduce aldimines and ketimines. Recently, ketimines, α-imino esters, and quinolines were reduced with high enantioselectivity through the combined use of a Hantzsch ester and chiral phosphoric acids.[7,8]

Metallacarboranes are a vast family of metallocene-type complexes that consist of at least one carborane cage and one or more metal cations.[9,10] Carborane clusters are versatile and efficient ligands for cations of metals such as Co, Fe, Ni, Cr, Re, Al, Au, Cu, Ir, Mn, and Pt. Metallacarboranes resemble metallocene-based catalytic systems but with cyclopentadienyl ligands replaced by carboranyl units. However, compared to metallocene-based catalytic systems, metallacarboranes have greater versatility and robustness. These advantages suggest that metallacarboranes have remarkable potential as catalysts that can be tailored to specific needs. A typical metallacarborane is a sandwich of two dicarbollide ($[C_2B_9H_{11}]^{2-}$) clusters with a metal ion in the center. $[C_2B_9H_{11}]^{2-}$ behaves as a Z5 ligand and is considered isolobal to the cyclopentadienyl (Cp^-) ligand that is present, for example, in ferrocene. *Exo*-metallated carboranes, as well as metallacarboranes with metal centers covalently bound into a carborane cage, have been extensively explored as catalysts in several types of reactions.[11–13] However, the potential of the metal bis(dicarbollide) sandwich-type metallacarboranes remains unexplored. Here, we describe a novel Brønsted acid type catalyst constructed from a cobalt bis(dicarbollide) complex, which provides a three-dimensional platform to which a phosphoric acid diester system can be attached that could serve as a catalytic unit and offer a high catalytic efficacy.



Scheme 1 Reduction of ketimines **3a**–**k** to the corresponding amines **4a**–**k** by using the phosphoric acid bridged cobalt bis(dicarbollide) ion (**1**) as a catalyst and the Hantzsch ester **2** as a hydrogen donor: **3a**: Ar^1 = 4-ClC_6H_4, Ar^2 = 4-$MeOC_6H_4$, R = Me; **3b**: Ar^1 = Ph, Ar^2 = 4-$MeOC_6H_4$, R = Me; **3c**: Ar^1 = 4-MeC_6H_4, Ar^2 = 4-$MeOC_6H_4$, R = Me; **3d**: Ar^1 = 4-$MeOC_6H_4$, Ar^2 = 4-$MeOC_6H_4$, R = Me; **3e**: Ar^1 = 2-naphthyl, Ar^2 = 4-$MeOC_6H_4$, R = Me; **3f**: Ar^1 = 4-ClC_6H_4, Ar^2 = Ph, R = Me; **3g**: Ar^1 = Ph, Ar^2 = Ph, R = Me; **3h**: Ar^1 = Ph, Ar^2 = 4-$MeOC_6H_4$, R = H; **3i**: Ar^1 = Ph, Ar^2 = 4-$ClOC_6H_4$, R = H; **3j**: Ar^1 = Ph, Ar^2 = 3,4,5-$(MeO)_3C_6H_4$, R = Me; **3k**: Ar^1 = Ph, Ar^2 = 4-ClC_6H_4, R = CO_2Me.

The monoanionic deltahedral metallacarborane cluster, [(1,2-dicarba-*closo*-undecaborane)-3,3′-cobalt(–1)(1′,2′-dicarba-*closo*-undecaborane)]ate {[3,3′-Co(1,2-$C_2B_9H_{11})_2]^-$}, is the most extensively investigated member of the metallabisdicarbollide family of type $[M(C_2B_9H_{11})_2]^{n-}$. Interest in $[3,3'\text{-}Co(1,2\text{-}C_2B_9H_{11})_2]^-$ initially emerged due to its capacity to extract ^{137}Cs and ^{90}Sr from nuclear waste[14,15] as well as its resistance to radiolysis and degradation in the presence of a concentrated

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strong acid, which is needed for the compound to remain intact in the presence of high-level nuclear waste.

Indeed, the chemistry and applications of metallacarboranes are relevant beyond the context of nuclear waste extraction. The virtues of metallacarboranes as a catalyst platform include a high chemical and thermal stability as well as easy charge and redox potential tuning and chemical modifications.

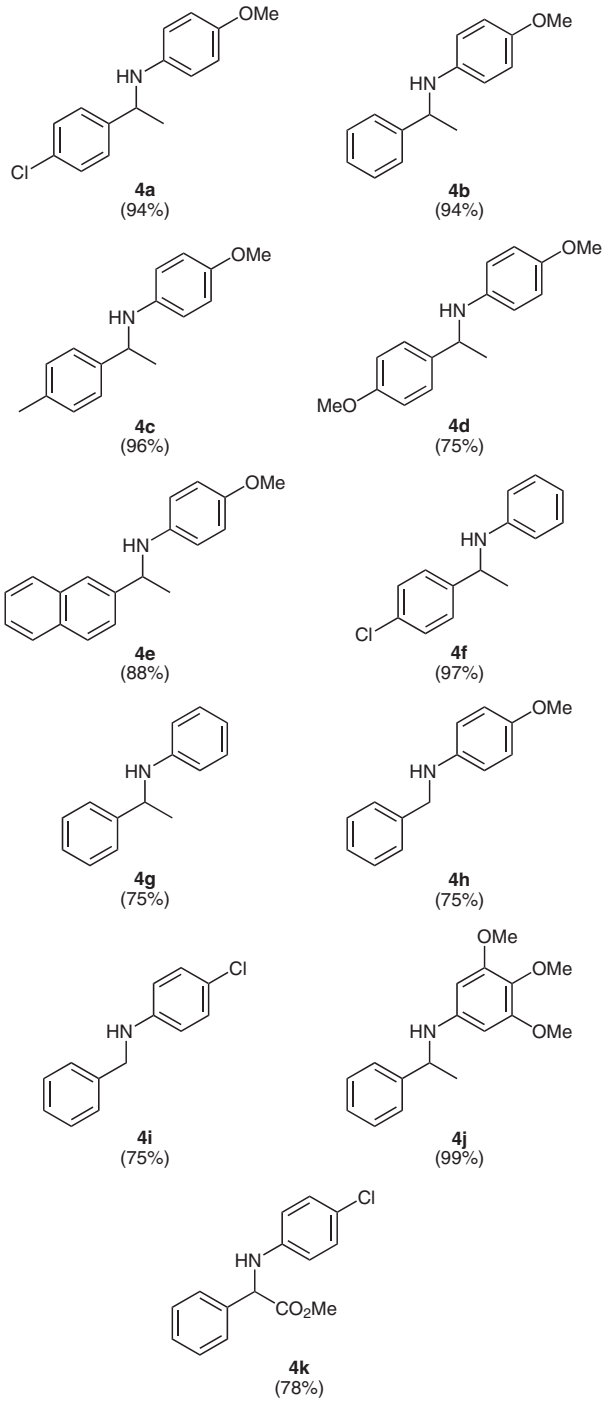

Figure 1 Substrate scope and yields of reduction of ketimines **3a**–**k** to amines **4a**–**k** by using phosphoric acid bridged cobalt bis(dicarbollide) ion (**1**) as catalyst

Recently, these compounds were studied for their utility as boron donors for Boron Neutron Capture Therapy (BNCT),[16,17] electrochemical labels,[18,19] anticancer[20,21] and antiviral agents,[22,23] and others. The properties of a metallacarborane can be adjusted by derivatizing the boron cluster ligands and changing the type of coordinate metal.[11] As an example of the exceptional potential of this class of boron cage compounds, we have examined metallacarborane derivatives as a scaffold for new catalysts; the results are described herein.

8,8′-μ-Phosphate[(1,2-dicarba-*closo*-undecaborane)-3,3′-cobalt(–1)(1′,2′-dicarba-*closo*-undecaborane)]ate, the triethylammonium salt **1**($HNEt_3^+$)$_2$ and the free phosphoric acid form **1**($HNEt_3^+$)(H^+) were prepared from the corresponding chlorophosphate according to a reported procedure.[14] Upon treatment of ketimine **3a**, which was derived from acetophenone and *p*-anisidine, with the Hantzsch ester **2** in the presence of phosphoric acid **1**($HNEt_3^+$)(H^+) and 5 Å MS in benzene at 50 °C for 24 h, the transfer hydrogenation of ketimine proceeded smoothly to furnish the corresponding amine **4a** in 94% yield (Figure 1, Scheme 1). A range of ketimines were subjected to the same reaction conditions to give the corresponding amines in high chemical yields[24] (**4b**–**f** and **4j**). Aldimines also proved to be suitable substrates (**4h** and **4i**). In addition, the α-imino ester underwent transfer hydrogenation to provide the corresponding α-amino ester in good yield (**4k**). The structures of these compounds were determined on the basis of their ^{1}H and ^{13}C NMR spectra.[25]

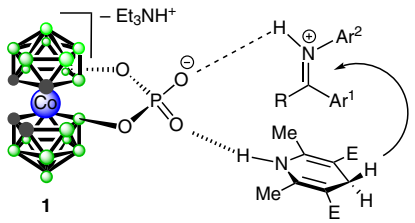

Figure 2 A possible transition state of the hydrogen transfer reaction catalyzed by the phosphoric acid bridged cobalt bis(dicarbollide) ion **1** in the presence of the Hantzsch ester **2**; E = CO_2Et

A screen of the reaction conditions revealed that the catalyst loading could be reduced to 5 mol% without compromising the yield, using only a 40% molar excess of the Hantzsch ester **2**. The turnover number (TON) of **1** was 10, which was lower than that for metal-catalyzed hydrogenation and similar to that obtained for organocatalysts. The reactivity of **1** was compared to the reactivity of a representative Brønsted acid catalyst comprising a phosphoric acid derived from BINOL and bearing a 2,4,6-(i-Pr)$_3$C$_6$H$_2$ group at the 3,3′-position. The reactions were conducted at 50 °C for 95 min to afford amine **4a** in 70 and 85% yield, respectively. These results showed that the catalytic activity toward the reduction of the aromatic imine was somewhat lower for **1** than for the BINOL-derived catalyst. Further modifications of **1** can be envisioned that may improve its catalytic activity.

A possible three-component transition state for the reaction catalyzed by **1** is shown in Figure 2. A previous DFT study[26] found that the *Z*-isomer (Ar^1 and Ar^2 in the *syn* conformation) was favored.

In conclusion, a new catalyst for the hydrogenation of aromatic ketimines based on a metallabisdicarbollide-type structural scaffold bearing a phosphoric acid bridge was proposed. In the presence of this catalyst, the hydrogenation of a range of substrates was achieved in high yield. The versatility of the metallacarborane structure and chemistry opens the way for the further development of this new type of Brønsted acid catalyst.

Acknowledgment

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(24) **Preparation of 4a–k; General Procedure:** All the reaction flasks were dried by flame, and all reactions were carried out under N_2. All the solvents were distilled under nitrogen and stored over 4 Å MS prior to use. Thin-layer chromatography was performed on Merck 60 F_{254} silica gel plates and visualization was accomplished by irradiation with UV light or by treatment with a solution of phosphomolybdic acid solution followed by heating. Ketimine **3a–k** (13.0 mg, 0.05 mmol), **1**($HNEt_3^+$)(H^+) (1.1 mg, 0.0025 mmol), and Hantzsch ester (**2**; 0.07 mmol, 1.4 equiv) were mixed in benzene (1 mL) in a flame-dried test tube containing dried molecular sieves (5 Å, 50 mg) under a nitrogen atmosphere at 50 °C for 20 h (not optimized). The resulting mixture was filtered through Celite (washed with CH_2Cl_2) and then evaporated under reduced pressure. The residue was purified by preparative silica gel thin-layer chromatography (hexane–EtOAc, 5:1 v/v).
(25) NMR characteristics of **4a–k**: NMR spectra were recorded with a Unity Inova-400 instrument (Varian Ltd., 400 MHz for ^1H, 100 MHz for ^{13}C) using $CDCl_3$ as solvent. Chemical shifts (δ) for ^1H were referenced to tetramethylsilane (δ = 0.00 ppm) as an internal standard. Chemical shifts (δ) for ^{13}C were referenced to the solvent signal ($CDCl_3$; δ = 77.00 ppm).
***N*-(4-Methoxyphenyl)-1-(4-chlorophenyl)ethylamine (4a):**[27] Yield: 94%; pale-yellow oil.^1H NMR (400 MHz, $CDCl_3$): δ = 1.47 (d, *J* = 6.8 Hz, 3 H), 3.69 (s, 3 H), 4.37 (q, *J* = 6.8 Hz, 1 H), 6.42–6.46 (m, 2 H), 6.66–6.71 (m, 2 H),

7.24–7.32 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.1, 53.8, 55.7, 114.6, 114.7, 127.3, 128.7, 132.3, 141.1, 144.0, 152.1.

***N*-(4-Methoxyphenyl)-1-phenylethylamine (4b):**[27] Yield: 94%; pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.50 (d, *J* = 6.8 Hz, 3 H), 3.69 (s, 3 H), 4.41 (q, *J* = 6.8 Hz, 1 H), 6.45–6.50 (m, 2 H), 6.66–6.71 (m, 2 H), 7.19–7.24 (m, 1 H), 7.29–7.38 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.0, 54.4, 55.7, 114.7, 114.7, 125.9, 126.8, 128.6, 141.3, 145.3, 152.0.

***N*-(4-Methoxyphenyl)-1-(4-methylphenyl)ethylamine (4c):**[27] Yield: 96%; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.47 (d, *J* = 6.8 Hz, 3 H), 2.32 (s, 3 H), 3.69 (s, 3 H), 4.37 (q, *J* = 6.8 Hz, 1 H), 6.45–6.50 (m, 2 H), 6.66–6.71 (m, 2 H), 7.11 (d, *J* = 8.0 Hz, 2 H), 7.24 (d, *J* = 8.0 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.0, 25.1, 53.9, 55.7, 114.5, 114.7, 125.8, 129.2, 136.3, 141.6, 142.4, 151.8.

***N*-(4-Methoxyphenyl)-1-(4-methoxyphenyl)ethylamine (4d):**[27] Yield: 75%; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.47 (d, *J* = 6.8 Hz, 3 H), 3.69 (s, 3 H), 3.78 (s, 3 H), 4.36 (q, *J* = 6.8 Hz, 1 H), 6.46–6.51 (m, 2 H), 6.67–6.71 (m, 2 H), 6.83–6.87 (m, 2 H), 7.25–7.29 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.0, 53.6, 55.2, 55.7, 113.9, 114.6, 114.7, 126.9, 137.4, 141.6, 151.8, 158.4.

***N*-(4-Methoxyphenyl)-1-naphthaylethylamine (4e):**[27] Yield: 88%; off-white sticky oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.57 (d, *J* = 6.8 Hz, 3 H), 3.67 (s, 3 H), 4.56 (q, *J* = 6.8 Hz, 1 H), 6.50–6.56 (m, 2 H), 6.64–6.70 (m, 2 H), 7.40–7.47 (m, 2 H), 7.48–7.52 (m, 1 H), 7.78–7.82 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.1, 54.5, 54.5, 55.7, 114.8, 124.3, 124.4, 125.5, 125.9, 127.6, 127.8, 128.4, 132.7, 133.6, 141.4, 142.9, 152.0.

***N*-Phenyl-1-(4-chlorophenyl)ethylamine (4f):**[28] Yield: 97%; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.46 (d, *J* = 6.7 Hz, 3 H), 4.38 (q, *J* = 2.2 Hz, 1 H), 6.45 (d, *J* = 7.6 Hz, 2 H), 6.63 (t, *J* = 7.4 Hz, 1 H), 7.06–7.12 (m, 2 H), 7.21–7.30 (m, 4 H), 7.48–7.52 (m, 1 H), 7.78–7.82 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.4, 53.2, 113.4, 117.3, 129.0, 129.3, 132.6, 144.1, 147.2.

***N*-(Phenyl)-1-phenylethylamine (4g):**[27] Yield: quant.; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.51 (d, *J* = 6.8 Hz, 3 H), 4.10 (br s, 1 H), 4.47 (q, *J* = 6.8 Hz, 1 H), 6.50 (d, *J* = 8.4 Hz, 2 H), 6.62–6.68 (m, 1 H), 7.06–7.12 (m, 2 H), 7.19–7.26 (m, 1 H), 7.28–7.40 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.9, 53.5, 113.3, 117.2, 125.8, 126.8, 128.6, 129.1, 145.1, 147.2.

***N*-Benzyl-4-methoxybenzenamine (4h):**[29a,b] Yield: 98%; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.74 (s, 3 H), 4.28 (s, 2 H), 6.60 (d, *J* = 7.6 Hz, 2 H), 6.77 (d, *J* = 7.6 Hz, 2 H), 7.24–7.38 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 49.5, 56.0, 114.3, 115.1, 127.4, 127.8, 128.8, 139.9, 142.6, 152.4.

***N*-Benzyl-4-chlorobenzenamine (4i):**[30] Yield: 95%; white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.14 (br s, 1 H), 4.31 (s, 2 H), 6.54–6.59 (m, 2 H), 7.10–7.15 (m, 2 H), 7.27–7.34 (m, 1 H), 7.34–7.39 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 48.3, 113.9, 122.1, 127.3, 127.4, 128.7, 129.0, 138.8, 146.5.

***N*-(3,4,5-Trimethoxyphenyl)-1-phenylethylamine (4j):**[31] Yield: 99%; pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.51 (d, *J* = 6.8 Hz, 3 H), 3.67 (s, 6 H), 3.71 (s, 3 H), 4.03 (br s, 1 H), 4.42 (q, *J* = 6.8 Hz, 1 H), 5.75 (s, 2 H), 7.19–7.25 (m, 1 H), 7.29–7.35 (m, 2 H), 7.35–7.39 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.9, 54.1, 55.6, 60.9, 90.8, 125.7, 126.9, 128.6, 129.7, 144.0, 145.3, 153.6.

Methyl (4-Chlorophenylamino)phenylacetate (4k):[32] Yield: 78%; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.73 (s, 3 H), 5.03 (s, 1 H), 6.47 (d, *J* = 8.8 Hz, 2 H), 7.06 (d, *J* = 8.8 Hz, 2 H), 7.31–7.37 (m, 3 H), 7.45–7.47 (m, 2 H).^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.9, 60.7, 114.5, 122.8, 127.2, 128.5, 128.9, 129.1, 137.7, 144.3, 172.0.

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