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Cobalt-catalyzed transfer hydrogenation of C=O and C=N bonds[†]

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An earth-abundant metal cobalt catalyst has been developed for the transfer hydrogenation of ketones, aldehydes, and imines under mild conditions. Experiments are described which provide insights into the mechanism of the transfer hydrogenation reaction.

Transition metal-catalyzed transfer hydrogenation is a simple and versatile method for the reduction of polar multiple bonds. A number of high-value chemical products, including alcohols and amines, can be efficiently produced using transfer hydrogenation processes.¹ Rapid turnover frequencies and high substrate to catalyst ratios have been achieved using catalysts based on ruthenium, iridium, and rhodium metals.2-6 However, for more widespread or industrial applications, catalysts composed of inexpensive, earthabundant metals would be preferable. Several iron-based systems have recently emerged for the transfer hydrogenation of ketones and imines,7-9 including a highly effective PNNP-ligated Fe catalyst for asymmetric transfer hydrogenation under mild conditions.¹⁰ Despite these advances, transfer hydrogenation catalysts composed of first-row transition metals remain scarce relative to their precious metal analogues. The discovery of additional examples of earthabundant metal transfer hydrogenation catalysts could open new ground for catalyst design, broadening the scope of potential catalytic systems and mechanisms.

Previously, we reported the synthesis of the square planar cobalt(II) alkyl complexes (PNP^{Cy})Co(CH_2SiMe_3) (1) and [($PNHP^{Cy}$)-Co(CH_2SiMe_3)]BAr^F₄ (2) and their use as pre-catalysts for hydrogenation (with H₂) (Fig. 1).¹¹ The efficacy of cobalt complex 2 as a hydrogenation catalyst suggested the potential of 2 as a catalyst for the transfer hydrogenation of polar multiple bonds.

Cobalt complexes 1 and 2 were first tested as catalysts for the transfer hydrogenation of acetophenone with isopropanol. Although the neutral cobalt(n) alkyl complex 1 showed no activity for the transfer hydrogenation reaction, complex 2 was found to be an active catalyst. In the reaction of acetophenone with isopropanol,



Fig. 1 Cobalt precatalysts evaluated for transfer hydrogenation.

1-phenylethanol was obtained in 94% isolated yield after 24 h at room temperature using 2 (2 mol%, generated *in situ* by the reaction of 1 and $H[BAr^{F_{4}}]$ ·(Et₂O)₂). No basic additives were required for this reaction.‡

Additional experiments were performed to assess whether the active cobalt catalyst was homogeneous or heterogeneous in nature. The transfer hydrogenation of acetophenone with isopropanol was carried out using 2 (2 mol%) with added Hg metal (100 equiv.). The catalytic activity was maintained in the presence of mercury, with the product 1-phenylethanol obtained in 90% GC yield after 24 h at room temperature. Another poisoning experiment was carried out using trimethylphosphine, inspired by the recent work of Morris and co-workers.12 Morris and co-workers found that heterogeneous iron nanoparticle catalysts for ketone transfer hydrogenation were unaffected by added Hg metal, but addition of PMe3 completely suppressed the catalytic activity.12 For the cobalt system, catalytic activity was maintained in the presence of PMe₃, consistent with a homogeneous catalyst. Even with 4 mol% added PMe₃, the transfer hydrogenation of acetophenone with isopropanol proceeded in 77% yield using the cobalt complex 2 (2 mol%) as a precatalyst.

Several different cobalt complexes were compared as precatalysts for the transfer hydrogenation reaction. In combination with $H[BAr^{F}_{4}] \cdot (Et_2O)_2$, the phenyl substituted PNP cobalt(II) alkyl

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derivative (PNP^{Ph})Co(CH₂SiMe₃) (3)^{11b} was slightly less active than cyclohexyl-substituted 2, affording 1-phenylethanol in 81% yield after 24 h at room temperature. Complex 4, having a BPh₄ counterion instead of BAr^F₄, displayed comparable activity for the transfer hydrogenation of acetophenone and isopropanol (1-phenylethanol was obtained in 92% isolated yield). The cobalt(m) complex 5^{11b} was also tested as a catalyst for the transfer hydrogenation of acetophenone, but it was found to be less effective, affording 1-phenylethanol in only 62% yield.

The substrate scope of the most active cobalt precatalyst 2 was then evaluated (Table 1 and Table S1, ESI[†]). Complex 2 (2 mol%) was a viable precatalyst for the transfer hydrogenation of aromatic ketones bearing electron donating or electron withdrawing substituents (Table 1, entries 1–4, Table S1, ESI[†]). The transfer hydrogenations of 2'-bromoacetophenone and 4'-methoxyacetophenone proceeded in high conversions within 24 h at room temperature, affording 1-(2-bromophenyl)ethanol and 1-(4-methoxyphenyl)ethanol in 95% and 99% isolated yields, respectively (entries 2 and 3). Aliphatic ketones were effectively reduced using a similar procedure; 2-hexanol was obtained in 95% GC yield from the transfer hydrogenation of 2-hexanone and isopropanol at 80 °C (entry 8). 4-*tert*-Butyl-cyclohexanone was reduced with 96% conversion, affording a mixture of *cis*- and *trans*-4-*tert*-butylcyclohexanol (33:67 ratio of *cis*: *trans*, entry 9).

Cobalt complex **2** was also an active precatalyst for the transfer hydrogenation of aldehydes. For aromatic aldehydes, transfer hydrogenation with isopropanol proceeded smoothly within 24 h at room temperature or 80 °C. For instance, benzyl alcohol and 2-fluorobenzyl alcohol were obtained in high yields (95% and 92% isolated yields, respectively) upon the transfer hydrogenation of benzaldehyde and 2-fluorobenzaldehyde with isopropanol using **2** (2 mol%). For conjugated substrates, such as *trans*-4-phenyl-3-buten-2-one or cinnamaldehyde, transfer hydrogenation with isopropanol resulted in the complete reduction of both C—C and C—O bonds.

The transfer hydrogenation of imines was also possible upon heating to 80 °C with pre-catalyst 2 (2 mol%). Several different aldimines underwent transfer hydrogenation with isopropanol, affording the corresponding amines in high yields within 24 h (95–98%, entries 14–16). Transfer hydrogenation of a ketimine, the *N*-benzyl imine of acetophenone, was unsuccessful, affording the reduced product in only 9% GC yield. Imine transfer hydrogenation has attracted considerable recent attention and has applications in the synthesis of amines.^{1d} Despite the importance of this reaction, there have been few prior examples of base metal catalysts for the transfer hydrogenation of imines.^{7a,10b,13}

Several additional experiments focused on gaining insights into the mechanism of the transfer hydrogenation reaction. Bäckvall and coworkers have identified "monohydride" and "dihydride" pathways for transition-metal catalyzed transfer hydrogenation reactions.¹⁴ To distinguish between these two possibilities, the transfer hydrogenation of acetophenone was carried out with both isopropanol- d_8 and isopropanol-OD (Fig. 2). While the reaction with isopropanol- d_8 afforded 1-phenylethanol- d_2 , the reaction with isopropanol-OD afforded 1-phenylethanol-OD, where less than 2% of deuterium was incorporated into the benzylic C–H position of the product. This suggests that the

Table 1 Substrate scope of the transfer hydrogenation reaction^a



^{*a*} Conditions: substrate (0.5 mmol) in isopropanol–THF (3:1 (v/v), 2 mL), 25 °C, 24 h. ^{*b*} Reactions run at 80 °C. ^{*c*} GC yield. ^{*d*} Ratio of cis:trans alcohol = 33:67.

transfer hydrogenation proceeds by a monohydride pathway, as scrambling of the deuterium into both the C–H and O–H positions would be expected for the dihydride pathway.

A number of precious metal transfer hydrogenation catalysts are proposed to operate by metal-ligand cooperativity, where catalysis is facilitated by a cooperative interaction between the metal center and an N–H group on the ligand.¹⁵ The proposed

Fig. 2 Deuterium labelling experiments support a "monohydride" pathway for the transfer hydrogenation reaction.

mechanisms typically involve outer-sphere reduction of the C=O or C=N bond in either a concerted or step-wise fashion.¹⁵ To evaluate the potential role of metal-ligand cooperativity in the cobalt transfer hydrogenation catalysis, the reactivity of 2 was compared with the analogue 6, where the central N-H group on the pincer ligand has been replaced with a methyl group. Complex 6 displayed similar, although slightly diminished activity relative to 2 for the transfer hydrogenation of acetophenone, affording 1-phenylethanol in 85% isolated yield after 24 h at RT. These results suggest that a metal-ligand cooperative interaction is not essential for the transfer hydrogenation catalysis. In addition, no chemoselectivity was exhibited by 2 in the transfer hydrogenation of conjugated substrates. In previous reports, a lack of chemoselectivity has often been associated with transfer hydrogenation catalysts that operate by an inner-sphere mechanism.^{1c} Overall, these results suggest that the mechanism of the cobalt-catalyzed transfer hydrogenation differs significantly from previously reported iron systems, which are proposed to react by an outersphere pathway involving metal-ligand cooperativity.^{10,16} The differences in mechanism between the cobalt catalyst and related iron catalysts may have important ramifications for future catalyst design.

Finally, when the transfer hydrogenation reaction was carried out in isopropanol- d_8 and monitored by ¹H NMR spectroscopy, no diamagnetic cobalt species were detected. This result, together with the lower activity of the cobalt(m) complex 5 in the transfer hydrogenation reaction, suggests that complex 5 is unlikely to be a catalyst resting state in the transfer hydrogenation reaction.

In conclusion, we have found that cobalt complex 2 is an active catalyst for the transfer hydrogenation of C—O and C—N bonds. Metal–ligand cooperativity is not required for the catalysis, which likely proceeds through a cobalt monohydride intermediate. This example of a homogeneous cobalt catalyst for transfer hydrogenation underscores the potential of cobalt complexes to be effective catalysts and expands the scope of possibilities for earth-abundant metal catalyst design.

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Notes and references

[‡] The addition of base did not promote cobalt catalyst **2**. Only 30% conversion was observed in the transfer hydrogenation of acetophenone and isopropanol with added KO^tBu (4 mol%). A 95% yield of 1-phenylethanol was obtained under the same reaction conditions using K_2CO_3 (4 mol%).

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