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Cobalt-Catalyzed Hydrogenation of Esters to Alcohols: Unexpected Reactivity Trend Indicates Ester Enolate Intermediacy**

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Abstract: *The atom-efficient and environmentally benign catalytic hydrogenation of carboxylic acid esters to alcohols has been accomplished in recent years mainly with precious-metal-based catalysts, with few exceptions. Presented here is the first cobalt-catalyzed hydrogenation of esters to the corresponding alcohols. Unexpectedly, the evidence indicates the unprecedented involvement of ester enolate intermediates.*

Reduction of esters to alcohols is a key industrial process for the production of agrochemicals, pharmaceuticals, flavors, and fragrances.[1] The reduction generally involves the use of stoichiometric amounts of metal hydride reagents, such as $LiAlH_4$, $NaBH_4$, and their derivatives, thus resulting in the generation of stoichiometric amounts of waste, low functional-group tolerance, and hazardous reagents.[2] In contrast, the catalytic hydrogenation of esters to alcohols is environmentally benign, waste-free, and fully atom-economical. Industrially, hydrogenations of fatty acid esters are achieved by using heterogeneous catalysts which require very high temperatures and pressures. To overcome these limitations some homogeneous catalytic systems for the hydrogenation of esters were reported.[3–5] In 2006, we reported the first mild, low-pressure hydrogenation of non-activated aromatic and aliphatic esters, catalyzed by a pincer ruthenium complex.[6] A year later, Firmenich researchers reported the hydrogenation of esters using bidentate amino phosphine or tetradentate imino phosphine ligands.[7] Since then, the catalytic hydrogenation of activated and non-activated esters and lactones has progressed rapidly and several bifunctional catalysts for this reaction have been developed.[8]

The replacement of expensive noble-metal catalysts by earth-abundant metal catalysts is an important goal. However, the tendency of first-row transition-metal complexes to react by one-electron pathways, rather than by the prevailing two-electron transformations of second- and third-row metals, can make it difficult to envisage and control catalytic reactivity.[9] Nevertheless, noteworthy progress has been made in the area of homogeneous earth-abundant metal hydrogenation catalysts.[10–12] Recently we and other groups have developed several iron-based catalysts for the hydrogenation of alkynes, ketones, aldehydes, and esters.[13] Very recently, substantial efforts were made towards the development of cobalt catalysts for homogeneous hydrogenation.[14,15] Chirik and co-workers developed diiminopyridine cobalt catalysts for olefin hydrogenation at room temperature,[14c] and for asymmetric hydrogenation of substituted styrenes.[14d] Hanson and co-workers developed an aliphatic PNP pincer cobalt(II) alkyl catalyst for the hydrogenation of aldehydes, ketones, imines, and alkenes, and dehydrogenation of secondary alcohols to ketones.[14a,b] However, the more demanding hydrogenation of ester derivatives by cobalt complexes has not been accomplished so far. Herein we report the first hydrogenation of esters catalyzed by a cobalt pincer complex. Unexpectedly, a mechanism involving ester enolate intermediacy is likely operative.

The complexes **1**,[16] **2**, and **3** (Figure 1) were synthesized by the treatment of $CoCl_2$ with 1.2 equivalents of the corresponding pincer ligand in THF. The new cobalt(II) complexes **2** and **3** were crystallographically characterized (Figure 2; see the Supporting Information for details). The complex **2** exhibits a trigonal bipyramidal structure, while the structure of **3** is close to a square pyramid, probably because of steric reasons involving the NEt_2 group.

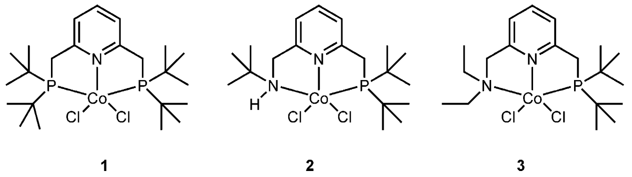

Figure 1. Cobalt pincer complexes.

Our initial attempts were focused on assessing the catalytic activity of the cobalt pincer complexes, upon activation with $NaHBEt_3$, for the hydrogenation of esters. Thus, the precatalyst **1** (2 mol%) was treated with 2 equivalents of $NaHBEt_3$ and used for the hydrogenation of

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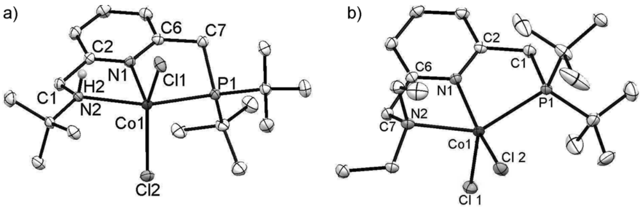
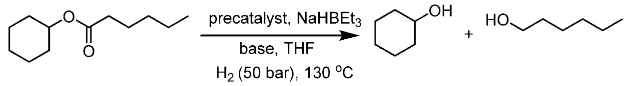


Figure 2. a) Molecular structure of **2** with thermal ellipsoids set at 50% probability. Hydrogens except H2 on the amine were omitted for clarity.[21] Selected bond lengths [Å] and angles [°]: Co1–N1 2.0902(13), Co1–N2 2.2679(12) Co1–Cl2 2.2938(5), Co1–Cl1 2.3027(5), Co1–P1 2.4938(4), N2–H2 0.85(2); N1-Co1-N2 76.71(5), N1-Co1-Cl2 128.81(4), N2-Co1-Cl2 97.28(4), N1-Co1-Cl1 104.02(4), N2-Co1-Cl1 89.38(4), Cl2-Co1-Cl1 126.934(17), N1-Co1-P1 79.83(4), N2-Co1-P1 156.49(3), Cl2-Co1-P1 96.295(16), Cl1-Co1-P1 97.656(16). b) Molecular structure of **3** with thermal ellipsoids set at 50% probability. Hydrogens were omitted for clarity. Selected bond lengths [Å] and angles [°]: Co1–N1 2.1783(11), Co1–N2 2.2430(12), Co1–Cl2 2.3081(4), Co1–Cl1 2.3244(4), Co1–P1 2.4724(4); N1-Co1-N2 75.88(4), N1-Co1-Cl2 160.77(3), N2-Co1-Cl2 97.72(3), N1-Co1-Cl1 95.99(3), N2-Co1-Cl1 97.71(3), Cl2-Co1-Cl1 102.877(14), N1-Co1-P1 78.04(3), N2-Co1-P1 142.37(3), Cl2-Co1-P1 98.075(14), Cl1-Co1-P1 111.639(14).

cyclohexyl hexanoate under 50 bar H_2 pressure at 130 °C in THF in the presence of 25 mol% *t*BuOK. Only 27% yield of cyclohexanol and 11% yield of 1-hexanol were obtained after 38 hours (Table 1, entry 1).

Table 1: Optimization of the reaction conditions for cobalt-catalyzed hydrogenation of esters.[a]



Entry	Precatalyst (mol%)	$NaHBEt_3$ (mol%)	Base (mol%)	*t* [h]	Solvent	Base	Yield [%][b]
1	**1** (2)	4	25	38	THF	*t*BuOK	27
2	**2** (2)	4	25	38	THF	*t*BuOK	85
3	**3** (2)	4	25	38	THF	*t*BuOK	67
4	**2** (4)	8	25	65	THF	*t*BuOK	88
5	**2** (2)	2	25	38	THF	*t*BuOK	65
6	**2** (4)	8	16	65	THF	*t*BuOK	70
7	**2** (4)	8	50	48	THF	*t*BuOK	99
8	**2** (4)	8	8	65	THF	*t*BuOK	20
9	**2** (4)	–	50	48	THF	*t*BuOK	50
10	**2** (1)	2	14	72	THF	*t*BuOK	54
11	**2** (2)	4	25	38	toluene	*t*BuOK	41
12	**2** (2)	4	25	38	1,4-dioxane	*t*BuOK	32
13	**2** (2)	4	25	38	THF	KHMDS	38
14	**2** (2)	4	25	38	THF	NaOMe	28
15	**2** (2)	4	25	38	THF	NaOEt	32

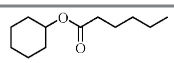
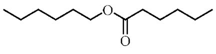
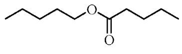
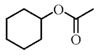
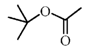
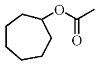
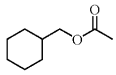
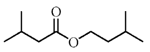
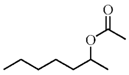
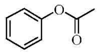
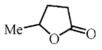
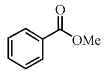
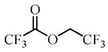
[a] Reaction conditions: ester (1.0 mmol), THF (1 mL), H_2 (50 bar), 130 °C. [b] Determined by GC with respect to cyclohexanol. THF = tetrahydrofuran.

Recently, we developed a pyridine-based PNNH/Ru complex with the potential for dual-mode metal–ligand cooperation, and it catalyzes the hydrogenation of esters at room temperature and low pressure.[17] Following this observation, the PNNH-based cobalt complex **2** was studied as a precatalyst for the hydrogenation of cyclohexyl hexanoate. To our delight, under similar reaction conditions used for the precatalyst **1**, **2** gave 85% yield of cyclohexanol with the formation of 79% hexanol (Table 1, entry 2). The complex **3**, under the same reaction conditions, gave a lower yield (67%) of cyclohexanol (entry 3). Increasing the loading of **2** to 4 mol% and the reaction time to 65 hours did not result in significantly higher yield of cyclohexanol (88%; entry 4). Activation of the **2** with only 1 equivalent of $NaHBEt_3$ gave a lower yield of cyclohexanol under similar hydrogenation conditions (entry 5). The amount of the base has a significant effect on the yield of the ester hydrogenation reaction. Increasing the precatalyst/base ratio to 1:12.5 increased the yield of cyclohexanol (99%), whereas decreasing the ratio to 1:2 gave only 20% product (entries 7 and 8). Without reacting the pre-catalyst with $NaHBEt_3$ only a moderate yield (50%) was obtained even at high precatalyst/base ratio (1:12.5; entry 9). Decreasing the precatalyst loading to 1 mol% gave 54% yield after 70 hours in the presence of 14 mol% base (entry 10). Among the different bases, *t*BuOK was found to be better than NaOMe, NaOEt, and potassium bis(trimethylsilyl)amide (KHMDS), and among the solvents screened, THF was a better choice than toluene or 1,4-dioxane (entries 11–15).

Next, the scope of the reaction was examined with various esters, including primary, secondary, and tertiary aliphatic esters. Thus, 1 mmol of cyclohexyl hexanoate under 50 bar pressure of H_2 at 130 °C in THF, in the presence of **2** (2 mol%) gave 85% yield of cyclohexanol and 79% yield of hexanol after 38 hours (Table 2, entry 1). A small amount of hexyl hexanoate was also observed as a result of the transesterification reaction between the formed hexanol and cyclohexyl hexanoate. Under similar reaction conditions, hexyl hexanoate gave 67% yield of hexanol after 43 hours. By increasing the precatalyst loading to 4 mol%, the yield of hexanol increased to 87% (entry 2). Similarly, pentyl pentanoate gave 67 and 85% pentanol by using 2 and 4 mol% precatalyst, respectively (entry 3). Under similar reaction conditions, other aliphatic esters also gave good yields of the hydrogenated product. γ-Valerolactone gave a moderate yield (50%) of 1,4-pentanediol (entry 11).

Aliphatic esters are normally considered to be more challenging substrates for catalytic hydrogenation than aromatic ones because of the generally higher electophilicity of the carbonyl carbon atom in the latter, thus making hydride transfer to the carbonyl group of aromatic esters more facile. Very surprisingly, this was not the case in the reactions reported here. Thus, methyl benzoate was not hydrogenated at all under similar reaction conditions. (Table 2, entry 12). Also, 2,2,2-trifluoroethyl trifluoroacetate, which is expected to be even more activated towards hydride transfer to the carbonyl group, remained unreacted (entry 13). In light of this unexpected inverse reactivity in the hydrogenation reaction we envisioned that the hydrogenation reaction might proceed by the enolate form of the ester, which is in equilibrium with the ester under the basic reaction conditions, and hence non-enolizable esters do not react. Mechanistically, the enolate can undergo hydrogenation to generate the salt of a hemiacetal intermediate which can form an aldehyde and alkoxide,

Table 2: Catalytic hydrogenation of esters using the cobalt precatalyst **2**.[a]

Entry	Ester	*t* [h]	Mol %	Product	Yield [%][b]
1		38	2	cyclohexanol hexanol	85 79
2		43	2	hexanol	67
		43	4	hexanol	87
3		48	2	pentanol	67
		48	4	pentanol	85
4[c]		48	2	cyclohexanol	61
5[c]		48	2	*tert*-butanol	67
6[c]		48	4	cycloheptanol	83
7[c]		48	4	cyclohexylmethanol	51
8		48	4	3-methylbutan-1-ol	65
		70	4	3-methylbutan-1-ol	80
9[c]		48	4	2-heptanol	52
10[c]		48	4	phenol	65
11		70	4	1,4-pentanediol	50
12		48	4	no reaction	–
13		48	4	no reaction	–

[a] Reaction conditions: substrate (1.0 mmol), precatalyst **2** (4 mol %), $NaHBEt_3$ (8 mol %), *t*BuOK (25 mol %), THF (1.0 mL), H_2 (50 bar), 130 °C. [b] Yields were determined by GC. [c] Yields of methanol and ethanol are not reported.

followed by hydrogenation of the aldehyde into the corresponding alcohol and regeneration of the catalytic base (Figure 3). This result also indicates that the organometallic mechanism likely involves insertion of the C=C bond into Co–H, rather than the expected hydride transfer to the carbonyl carbon atom. To our knowledge, such a mechanism of ester hydrogenation was not indicated before. It is particularly surprising, considering the very low concentration of the ester enol tautomer of simple esters.[18]

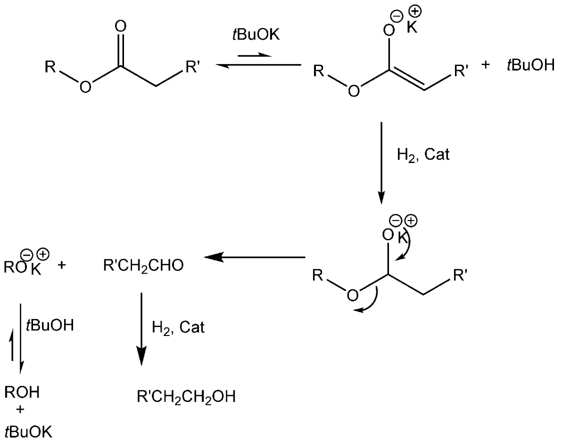


Figure 3. Plausible mechanism of ester hydrogenation via an ester enolate intermediate.

Regarding the active cobalt catalyst, we believe that under the reactions conditions a cobalt(I) hydride complex is formed. Indeed, Chirik and co-workers has shown that treatment of the complex $[(PNP)CoCl_2]$ (**1**) with one equivalent and two equivalents of $NaHBEt_3$ gave the cobalt(I) complexes $[(PNP)Co^ICl]$ and [(PNP)CoH], respectively.[19] We observed similar reactivity in the case of complexes **2** and **3**. Thus, treatment of **2** and **3** with one equivalent of $NaHBEt_3$ at room temperature gave the paramagnetic $[(PNNH)Co^ICl]$ and $[(PNNEt_2)Co^ICl]$. The complexes were characterized by X-ray crystallography (see the Supporting Information). Although we were not able to isolate the active catalyst in the ester hydrogenation reactions, we believe that in situ a catalytically active cobalt hydride pincer complex was formed by reaction with two equivalents of the hydride source and under H_2 pressure.[20]

In conclusion, we have demonstrated the first hydrogenation of esters into alcohols catalyzed by a cobalt complex. New $PNNEt_2$ and PNNH cobalt pincer complexes were prepared. The PNNH-based cobalt pincer complex was found to be the best catalyst. An unprecedented mechanism for ester hydrogenation, involving enolate intermediates, is indicated, thus suggesting selectivity for enolizable esters. The synthetic implications of this finding and the detailed mechanism of the reaction are being explored.

Keywords: alcohols · cobalt · esters · homogeneous catalysis · hydrogenation

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[20] [(PNNH)Co^{I}Cl] catalyzes the hydrogenation of cyclohexyl hexanoate less efficiently than the presumably formed in situ cobalt(I) catalyst (68% yield of cyclohexanol under the same conditions).

[21] CCDC 1048654 (**3**), 1048655 (**2**), 1048656 [(PNNH)CoCl], and 1048657 [(PNNEt$_2$)CoCl] contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Homogeneous Catalysis

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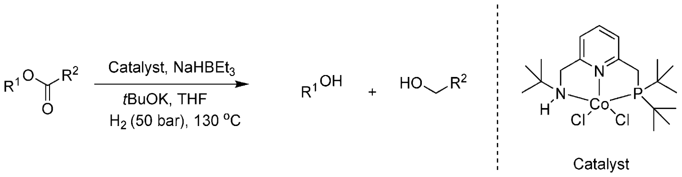
Cobalt-Catalyzed Hydrogenation of Esters to Alcohols: Unexpected Reactivity Trend Indicates Ester Enolate Intermediacy



Getting involved: The atom-efficient and environmentally benign catalytic hydrogenation of carboxylic acid esters to alcohols has been accomplished in recent years mainly with precious-metal-based catalysts. Presented here is the first cobalt-catalyzed hydrogenation of esters to alcohols. Unexpectedly, the evidence indicates the unprecedented involvement of ester enolate intermediates.