Hydrogenation of carboxylic acids with a homogeneous cobalt catalyst

Korstanje, T.J.; van der Vlugt, J.I.; Elsevier, C.J.; de Bruin, B.

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Hydrogenation of carboxylic acids with a homogeneous cobalt catalyst

Ties J. Korstanje, Jarl Ivar van der Vlugt, Cornelis J. Elsevier, Bas de Bruin

The reduction of esters and carboxylic acids to alcohols is a highly relevant conversion for the pharmaceutical and fine-chemical industries and for biomass conversion. It is commonly performed using stoichiometric reagents, and the catalytic hydrogenation of the acids previously required precious metals. Here we report the homogeneously catalyzed hydrogenation of carboxylic acids to alcohols using earth-abundant cobalt. This system, which pairs Co(BF4)2·6H2O with a tridentate phosphine ligand, can reduce a wide range of esters and carboxylic acids under relatively mild conditions (100°C, 80 bar H2) and reaches turnover numbers of up to 8000. There is great interest among the pharmaceutical and fine-chemical industries in finding more sustainable methods to reduce moieties such as esters and carboxylic acids to alcohols. In the emerging field of biomass feedstock conversion to produce high-value chemicals, the reduction of these abundantly available oxygen-containing functional groups is also of crucial importance. Traditionally, esters and carboxylic acids are reduced using stoichiometric reagents, such as aluminum- or borohydrides, but these pose an inherent safety risk and produce large amounts of waste material (1). Selective catalytic hydrogenation of esters and carboxylic acids to the corresponding alcohols could facilitate the synthesis of many products in various sectors of the chemical industry; for instance, it could facilitate the conversion of (biomass-derived) succinic acid into the industry; for instance, it could facilitate the conversion of (biomass-derived) succinic acid into the

iron-based catalysts for the hydrogenation of esters have been reported (22–24). Here we present a cobalt-based catalytic system capable of hydrogenating both esters and carboxylic acids to the corresponding alcohols, using H2 as the reductant. The catalyst is generated in situ from a Co(BF4)2·6H2O precursor and the triphos ligand, which are both commercially available, making this method highly suitable for use in practical organic synthesis and biomass conversion.

Initially, various cobalt precursors were tested, in combination with the triphos ligand, in the hydrogenation of methyl benzoate to yield benzyl alcohol and methanol. Combining methyl benzoate with 10 mole percent (mol %) of the metal precursor and the triphos ligand in distilled methanol, under 80 bar of initial H2 pressure and at 100°C reaction temperature, produced only minor amounts of alcohol with cobalt(III) acetylacetonate, cobalt(II) acetylacetonate, and cobalt(II) acetate (table S1). Using Co(BF4)2·6H2O as the metal precursor resulted in almost full substrate conversion within 5 hours, providing the desired benzyl alcohol in excellent yield. Decreasing the catalyst loading to 5 mol % resulted in full conversion within 22 hours, with a good yield of benzyl alcohol. Lower catalyst loadings required very long reaction times (2 mol %, 94 hours) or led to lower overall activity (1 mol %). Based on this initial catalyst optimization, the substrate scope of the Co(BF4)2·6H2O and triphos (Co/triphos) hydrogenation system was investigated (Table 1 and table S2). Using tert-butylbenzoate, an ester substrate that has low activity with many catalysts due to the steric hindrance of the tert-butyl group, full conversion was obtained within 5 hours. Also, with aliphatic esters such as methyl butyrate and methyl 3-trans-hexenoate, good yields of the fully reduced corresponding alcohol were obtained within 22 hours. Hydrogenation of γ-valerolactone, a substrate that can easily be obtained from biomass and, as such, is of interest for biomass valorization, produced 2-methyltetrahydrofuran and 1,4-pentanediol in good yields. These products have attracted attention for their respective applications as a fuel additive and as a monomer for polyester production (2). A long-chain fatty acid methyl ester and even a triglyceride could also be smoothly hydrogenated to obtain the corresponding reduced fatty alcohol in good yields, using the Co/triphos system.

Van ‘t Hoff Institute for Molecular Sciences, University of Amsterdam, Science Park 904, 1098 XH Amsterdam, Netherlands. *Corresponding author. E-mail: c.j.elsevier@uva.nl (C.J.E.); b.debruin@uva.nl (B.d.B).
The successful application of the Co/triphos system for ester hydrogenation led us to investigate its efficacy in the more challenging conversion of carboxylic acids (Table 2). Using benzoic acid as the substrate, with 2.5 mol% catalyst loading and THF as the solvent (to prevent in situ esterification and thus to ensure that the system is truly hydrogenating acids), benzyl alcohol was obtained in good yield within 22 hours. Removal of any remaining acid starting material and the majority of the catalyst can be easily accomplished by washing with a saturated aqueous sodium carbonate solution. Further purification using column chromatography yielded the isolated alcohol product. Increasing the catalyst loading to 5 mol% led to full conversion after 4 hours, compared with 22 hours for methyl benzoate. This indicates that hydrogenation of carboxylic acids with the Co/triphos system outcompetes the conversion of the corresponding carboxylic esters, which is surprising, considering the difficulties associated with hydrogenating carboxylic acids in most systems. The system tolerates several functional groups, such as chlorides, fluorides, trifluoromethyls, and hydroxides, which can be used for further synthetic processing, such as C-C cross-coupling. More labile groups such as bromide, iodide, boronate, and methoxy functionalities undergo (partial) defunctionalization, but they do not hamper the reactivity (Table S3).

Furthermore, the catalytic system is capable of hydrogenating a wide scope of carboxylic acid substrates, including aromatic and long- and short-chain aliphatic acids, all of which are smoothly hydrogenated to the corresponding alcohols. From a biomass viewpoint, the direct hydrogenation of levulinic acid to 2-methyltetrahydrofuran and 1,4-pentanediol is relevant, because it eliminates the need to isolate γ-valerolactone as the cyclic ester intermediate. The hydrogenation of succinic acid is also of interest, because it produces 1,4-butanediol, which is a comonomer in the production of polyesters such as polybutylene terephthalate. Furthermore, polymerization of 1,4-butanediol with (potentially biomass-derived) succinic acid constitutes a completely biomass-derived route to polybutylene succinate. In our system, short-chain acids are hydrogenated more easily than long-chain acids, which is in agreement with previous research on acid hydrogenation (20). Moreover, it is possible to reduce the liquid acids under solventless conditions, allowing low catalyst loadings (down to 0.1 mol%) for butyric acid and acetic acid, while still giving good yields of 1-butanol and ethanol, respectively. Under these conditions, esterification of the carboxylic acid starting material by the alcohol product also takes place, as demonstrated by the observation of butyl butyrate and ethyl acetate, respectively. When using formic acid or trifluoroacetic acid, neat conditions did not produce any alcohol, probably because of the high polarity of these acids. With THF as the solvent, however, a very low catalyst amount of 125 parts per million can be used for trifluoroacetic acid, while still reaching full conversion in 22 hours and giving a good yield of 50% of trifluoroethanol (the remaining mass balance consists of trifluoroethyl trifluoroacetate and an unidentified side product). Hydrogenation of formic acid in THF also proceeds smoothly, but it requires a somewhat higher catalyst loading of 0.25 to 0.5 mol%.

In comparison with the reported P. furiosus biocatalytic system (5), which uses a reaction temperature of 40°C and 5 bar H2 pressure, our system generally has a lower activity and requires harsher reaction conditions; however, it is able to convert a much wider substrate scope and can obtain higher conversions of the carboxylic acid within the same period of time. Relative to our
system, noble metal–based heterogeneous catalysts such as Ru-Sn/Al2O3 and Pt-Re/TiO2, operating at temperatures of 240° and 130°C and pressures of 80 and 20 bar, respectively, give slightly lower conversions (82%), higher reducing numbers of stearic acid (512 and 97, respectively), and a lower selectivity due to the formation of decarboxylation and dehydration products. Furthermore, leaching of tin occurs when using the former catalyst, which is highly undesirable for a pharmaceutical application, and the Pt-Re/TiO2 catalyst suffers from aromatic ring hydrogenation when using aromatic substrates. In comparison with previously reported homogeneous catalysts, our cobalt-based system outperforms both the ruthenium- and iridium-based systems for acid hydrogenation (19, 20): The ruthenium-based system operates at much higher temperatures (140° to 220°C) and with higher catalyst loadings (>2 mol %) than our system, and the iridium-based system requires a higher reaction temperature (120° versus 100°C) and much longer reaction times (65 versus 22 hours) to produce similar turnover numbers with acetic acid (777 for iridium versus 780 for cobalt).

To investigate the specificity of the triphos ligand, different ligand systems were tested. The tridentate analog tetraphos [P(CH2CH2PPh2)3], known to be active in CO2 hydrogenation in combination with cobalt (27), did not show any activity in ester hydrogenation. In addition, the combination of various bidentate phosphines with monodentate phosphines did not show any reactivity for either esters or acids. The influence of additives was investigated, but neither acid nor base had a positive effect on the reactivity in the ester hydrogenation reaction, nor did an additional reducing agent, such as zinc dust (10). The analogous cobalt precursor [Co(NCCH3)6][BF4]2 in combination with triphos, also did not show any activity in ester or acid hydrogenation under dry conditions. However, when methyl benzoate was used as the substrate, the activity was restored by adding six equivalents of water (relative to the catalyst), and [Co(THF)3][BF4]2 showed carboxylic acid conversion under dry conditions. The activity of the [Co(NCCH3)6][BF4]2 precursor in the absence of water was probably caused by the stronger coordination of the acetonitrile ligands, which hampers reactivity under dry conditions.

The known dinuclear cobalt trishydride complex [Co2(triphos)3(H)3][BF4]2 also was found to be inactive in this reaction. The inactive cobalt precursor Co(OAc)2·4H2O (OAc, acetate) could be activated by the addition of two equivalents of BF3·OEt2 or [HBF4]− and, different ligand systems were tested. The tetradentate analog tetraphos [P(CH2CH2PPh2)3], known to be active in CO2 hydrogenation in combination with cobalt (27), did not show any activity in ester hydrogenation. In addition, the combination of various bidentate phosphines with monodentate phosphines did not show any reactivity for either esters or acids. The influence of additives was investigated, but neither acid nor base had a positive effect on the reactivity in the ester hydrogenation reaction, nor did an additional reducing agent, such as zinc dust (10). The analogous cobalt precursor [Co(NCCH3)6][BF4]2 in combination with triphos, also did not show any activity in ester or acid hydrogenation under dry conditions.

Fig. 2. Proposed mechanism for the Co/triphos–catalyzed hydrogenation of carboxylic acids to alcohols. BF4 anions are omitted for clarity. The central area shows the crystal structure of the proposed resting state, [Co(triphos)(H)3][BF4]. The numbers below the structures indicate the relative enthalpies (kcal mol−1) at 373 K, obtained from dispersion-corrected density functional theory (DFT-D3), using the BP86 functional, def2-TZVP basis set, and Grimme’s version 3 dispersion corrections (disp3). Colors in the central structure correspond to cobalt (blue), oxygen (red), phosphorus (yellow), and carbon (gray).

Further research is required to completely explain the observed counterion effect.

To further investigate the reaction mechanism, we performed partial poisoning studies using TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) as a radical inhibitor and TMTU (tetramethylthiourea) as a strongly binding poison (28). With both reagents, the reaction was completely inhibited by one equivalent per catalyst, and for TMTU, only half an equivalent was sufficient (fig. S1). This suggests that TMTU deactivates two cobalt centers, either by acting as a bridging poison ligand or by acting on a dinuclear cobalt species, whereas TEMPO poisons a monomeric cobalt species. Furthermore, this result excludes the formation of nanoparticles as the active catalyst, because this would require a much lower amount of poison for full inhibition of the catalysis (29). This result is consistent with a mercury poison test, which did not show any considerable inhibition of the catalysis.

We studied the reaction further by means of high-resolution electron spray ionization mass spectrometry (ESI-MS). Using benzoic acid as the substrate, a catalytic sample was analyzed after 1 hour of reaction time; the major signal detected (mass/charge ratio = 804.1875) has a mass consistent with that of a [Co(triphos)(benzoate)]+ species (fig. S2). The same species was detected upon separately mixing the cobalt precursor, triphos, and benzoic acid in a 1:1:1 ratio and heating.
this mixture briefly under an inert atmosphere. Because ESI-MS does not provide information on the oxidation state, we also performed in situ electron paramagnetic resonance (EPR) spectroscopy. The catalytic reaction was carried out in a high-pressure EPR tube, using 2-methyltetrahydrofuran as the solvent (to obtain a good glass) and 15 bar of H₂ pressure, followed by rapid cooling of the reaction mixture from 100°C to ~18°C (76 K) after 2 hours of reaction time. The EPR tube was subsequently cooled to 20 K in the EPR cavity to record the EPR spectrum. Two signals were observed: a broad signal, arising from a high-spin species (electron spin, $S = \frac{7}{2}$) and a well-defined signal from a low-spin species ($S = \frac{1}{2}$) with a complex hyperfine coupling pattern due to coupling with cobalt (nuclear spin, $I = \frac{1}{2}$) and three phosphorus atoms ($I = \frac{1}{2}$) (fig. S3). The high-spin species originated from a small excess amount of Co(BF₄)₂·6H₂O, whereas the low-spin species produced an identical signal to that of an independently prepared 1:1:1 mixture of Co(BF₄)₂·6H₂O, triphos, and benzoic acid (fig. S2). This confirms the results obtained by ESI-MS and also shows that the cobalt center in this species remains in the +2 oxidation state. Based on these results, we propose the mechanism depicted in Fig. 2.

The proposed mechanism starts with the formation of a precatalytic species, [Co₂(triphos)₄(μ-OH)₃](BF₄)₂, which is known to form spontaneously when Co(BF₄)₂·6H₂O and triphos are mixed (30). This dimer is split by the substitution of the hydroxyl ligand for an alkanoate, producing the catalytically active species [Co(triphos)(alkanoate)]BF₄, which is observed in EPR and ESI-MS and is known to be a stable species (30). By means of slow vapor diffusion of diethyl ether into a CH₂Cl₂ solution of the complex, we were also able to obtain single crystals that enabled x-ray crystal structure determination of this species as the BF₄⁻ salt. The complex was prepared by mixing Co(BF₄)₂·6H₂O, triphos, and benzoic acid in a 1:1:1 ratio in THF, followed by the addition of NaBPh₄ in a 10-fold excess amount. The x-ray crystal structure (Fig. 2 and table S5) shows the expected bidentate ($\nu^2$) binding mode of the benzoate and a slightly distorted square pyramidal structure around the cobalt center ($\tau = 0.11$ (31)), as expected for a low-spin cobalt(II) species. This species produces the same EPR spectrum as the catalytic mixture, confirming the Co(triphos)x⁵⁻(alkanoate) species as the resting state, but it was found to be inactive in catalysis because of the presence of the BPh₄⁻ anion (which has a deactivating effect on catalysis, as we also observed when NaBPh₄ was added to the catalytically active 1:1 mixture of triphos and Co(BF₄)₂·6H₂O).

From this Co(triphos)x⁵⁻(alkanoate) species, we propose that initial heterolytic hydrogen splitting occurs over the cobalt-O bond, followed by the migratory insertion of the hydride into the carbonyl carbon and a second heterolytic hydrogen splitting step over the cobalt(II) hydroxyalkanolate intermediate, thereby expelling one equivalent of water and producing the [Co(triphos)(H)(alkylolate)]⁺ species (32). A final hydride migration step, followed by proton transfer and ligand exchange with another carboxylic acid substrate, gives the desired alcohol and regenerates the active catalyst. This mechanism fits the ESI-MS and EPR results that show [Co(triphos)(OOCR)]⁺ as the resting state under catalytic conditions, and it also correlates well with the quantitative poisoning studies. The proposed mechanism is also supported by density functional theory (DFT) calculations (performed on the complete system, using acetic acid as the substrate; Fig. 2 and figs. S4 and S5), showing that the (lowest-energy) resting state is the Co(triphos)(H)(alkylolate) species. The overall calculated reaction barrier is 18.6 kcal mol⁻¹, which is a reasonable energy barrier for a reaction proceeding smoothly at 100°C. The rate-determining transition state involves hydride migration to the coordinated aldehyde, whereafter energetically favorable steps occur involving proton transfer and exchange of the product for a carboxylic acid substrate, thus resulting in an overall mildly exothermic reaction (~3.8 kcal mol⁻¹).

The results presented here describe the first catalytic system based on a cheap and abundant first-row transition metal that is capable ofhydrogenating carboxylic acids to the corresponding alcohols using molecular hydrogen as the reductant. Insight into the mechanism of this system was obtained by means of ESI-MS, in situ EPR, x-ray crystallography, and DFT calculations, all of which support a Co(triphos)x⁵⁻(alkanoate) resting state. The DFT calculations suggest a mechanism that involves heterolytic H₂ splitting over cobalt (II) alkanoate and cobalt(II) hydroxyalkanolate intermediates as key steps in the catalytic cycle.

### Table 2. Hydrogenation of carboxylic acids using Co(BF₄)₂·6H₂O and triphos.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Substrate</th>
<th>Product(s)</th>
<th>Substrate</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>5% (4h)</td>
<td>&gt;85 (65)</td>
<td>2.5%</td>
<td>&gt;99 (71)</td>
<td>5%</td>
<td>95 (92)</td>
</tr>
<tr>
<td>2.5%</td>
<td>&gt;85 (62 / 39)</td>
<td>10%</td>
<td>&gt;99 (ether: 14, diol: 47)</td>
<td>0.25%*</td>
<td>94 (81)</td>
</tr>
<tr>
<td>5%</td>
<td>&gt;99 (82 / 70)</td>
<td>2.5%</td>
<td>&gt;85 (lactone: 23, diol: 61)</td>
<td>0.5%</td>
<td>&gt;99 (76)</td>
</tr>
<tr>
<td></td>
<td>&gt;99 (96 / 84)</td>
<td>5%</td>
<td>&gt;99 (95)</td>
<td>0.1%*</td>
<td>53 (17 / 5)</td>
</tr>
<tr>
<td>5%</td>
<td>98 (98 / 82)</td>
<td></td>
<td></td>
<td>125 ppm</td>
<td>97 (50h)</td>
</tr>
<tr>
<td>5%</td>
<td>&gt;90 (89 / 66)</td>
<td></td>
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</tbody>
</table>

*Neat conditions. †36% GC yield and 24% isolated yield of butyl butyrate obtained. Isolated yields shown here are the amounts present in the isolated mixture of 1-butanol and butyl butyrate, because it proved difficult to separate these compounds by distillation (probably because of azotropic formation). ‡13% ethyl acetate obtained. §29% methyl formate formed. Based on fluorine-19 nuclear magnetic resonance. Mass balance is completed by an unknown side product.

### REFERENCES AND NOTES


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32. A similar structure with a PEt3 group instead of the acetaldehyde, [Co(triphos)(H)(PEt3)]BPh4, is described in (33).

ACKNOWLEDGMENTS
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SUPPLEMENTARY MATERIALS
www.sciencemag.org/content/350/6258/298/suppl/DC1
Materials and Methods
Figs. S1 to S39
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Cartesian Coordinates (XYZ Format) for All Calculated Structures
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