

Iron-Based Catalysts for the Hydrogenation of Esters to Alcohols

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Supporting Information

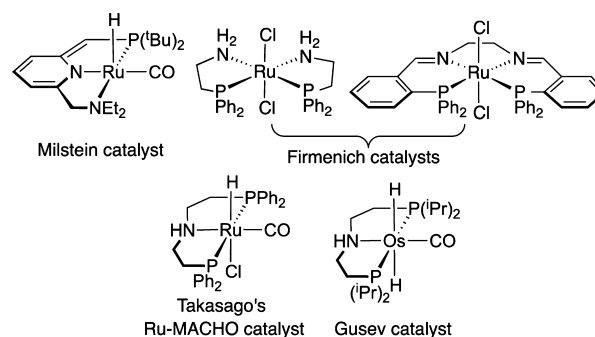
ABSTRACT: Hydrogenation of esters is vital to the chemical industry for the production of alcohols, especially fatty alcohols that find broad applications in consumer products. Current technologies for ester hydrogenation rely on either heterogeneous catalysts operating under extreme temperatures and pressures or homogeneous catalysts containing precious metals such as ruthenium and osmium. Here, we report the hydrogenation of esters under relatively mild conditions by employing an iron-based catalyst bearing a PNP-pincer ligand. This catalytic system is also effective for the conversion of coconut oil derived fatty acid methyl esters to detergent alcohols without adding any solvent.

Hydrogenation of esters is an industrially important process and is used to manufacture alcohols on a multimillion ton scale per annum for numerous applications. Long-chain primary or fatty alcohols, in particular, are widely used as precursors to surfactants, plasticizers, and solvents. In 2012, world consumption of fatty alcohols grew to 2.2 million metric tons, and the global demand was projected to increase at a compound annual growth rate of 3–4% from 2012 to 2020.¹ Currently, about 50% of fatty alcohols are considered “natural fatty alcohols” as they are produced through hydrogenation of fatty acid methyl esters that are derived from coconut and palm kernel oils, among other renewable materials. This process is typically accomplished by using a heterogeneous catalyst mainly consisting of copper chromite.² While effective, the copper chromite catalyst operates under very harsh reaction conditions (250–300 °C and 2000–3000 psig of H₂ pressure). As far as energy costs for operation and capital costs for new capacity are concerned, developing a homogeneous catalytic system for ester hydrogenation is highly desirable because of its potential to be effective under much milder conditions. Furthermore, substrate compatibility or functional group tolerance is expected to be higher with a homogeneous catalyst, and the hydrogenation technology could be more broadly applied to specialty chemical synthesis.

The development of homogeneous catalysts capable of hydrogenating esters has lagged way behind the research on hydrogenation of other carbonyl substrates such as aldehydes and ketones. This is mainly due to the fact that the carbonyl group in esters is less electrophilic than that in aldehydes and ketones. Studies prior to the early 2000s were primarily focused on dimethyl oxalate³ and fluorinated esters,⁴ which are

substantially more reactive esters than those without a strongly electron-withdrawing group (e.g., methyl benzoate and fatty acid methyl esters). Catalytic systems amenable to unactivated esters, however, still suffered from extreme reaction conditions.^{5,6} Major breakthroughs were made around 2006 by the Milstein group⁷ and Firmenich SA,^{8,9} which independently developed Ru-based catalysts for ester hydrogenation under relatively low temperatures and pressures. The Milstein catalyst features a pyridine-derived PNN-pincer ligand (Chart 1) and

Chart 1. Representative Homogeneous Catalysts for Ester Hydrogenation



operates at 115 °C under 63 psig of H₂ pressure. The Firmenich catalysts contain bidentate amino-phosphine or tetradentate imino-phosphine ligands and are effective at 60–100 °C under 130–710 psig of H₂ pressure. In both catalytic systems, metal–ligand cooperativity was thought to be critical for H₂ activation and/or reduction of the ester C=O bond. Since these two studies, many other Ru- or Os-based catalysts have been developed with the aim to improve catalyst efficiency;^{10–27} these results have been thoroughly discussed in recent reviews.^{28–30} One notable example is Takasago's Ru-MACHO catalyst, which was used to convert more than 2 t of (*R*)-lactate to (*R*)-1,2-propanediol with the stereocenter preserved.¹⁴ In this specific case, the hydrogenation reaction was carried out at ambient temperature under 565–594 psig of H₂ pressure. It is also worth mentioning that an osmium PNP-pincer complex developed by Gusev et al.³¹ was successfully used to catalyze the hydrogenation of saturated triglycerides to cetyl and stearyl alcohols at 220 °C under 935 psig of H₂ pressure.³²

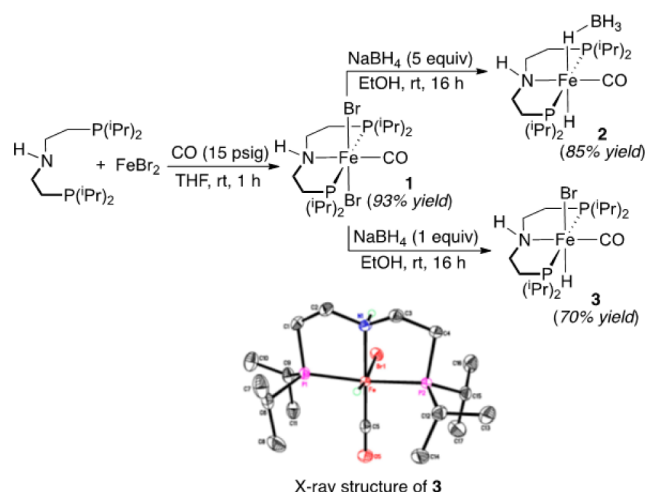
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Despite the progress, almost all ester hydrogenation catalysts developed to date contain a precious metal: ruthenium or osmium. This is reminiscent of the early stage of catalyst design for the hydrogenation of other unsaturated double bonds. In recent years, significant effort has been made to develop various reduction processes catalyzed by earth-abundant transition metals.³³ Within this context, iron has been a particularly attractive choice of metal for catalysis due to its low cost and low impact on the environment.³⁴ In terms of hydrogenation of esters to alcohols, we are aware of only one iron-based homogeneous catalytic system, which contains a pyridine-linked diphosphine ligand and was reported very recently by Milstein et al.³⁵ However, the substrates employed in this study are limited to fluorinated esters, which are significantly activated. In this paper, we report iron PNP-pincer complexes as efficient catalysts for the hydrogenation of a much broader range of esters. Most importantly, our catalytic system can be applied to fatty acid methyl esters that are widely used in industry and the reaction can be carried out without adding an external solvent.

Given the success of Ru-MACHO and Gusev catalysts, we sought to synthesize analogous iron pincer complexes 1–3 bearing a PNP-pincer ligand (Scheme 1). During the

Scheme 1. Synthesis of Iron PNP-Pincer Complexes



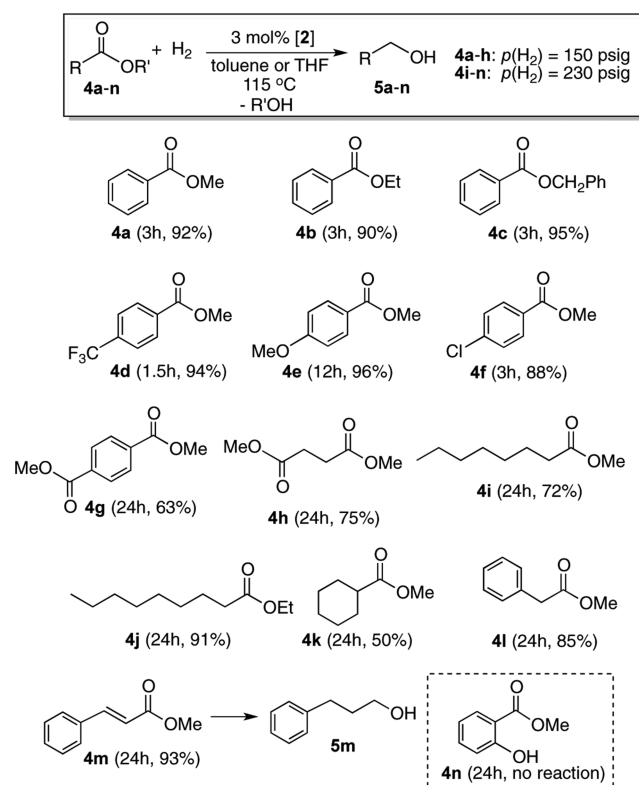
development of this project, Beller et al. also reported the synthesis of these compounds but used them as catalysts for the release of H₂ from methanol.³⁶ Meanwhile, Hazari, Schneider, and co-workers prepared compound **2** from the PNP-pincer ligand and FeCl₂.³⁷ In our laboratory, compounds 1–3 were synthesized by slightly different procedures. The *trans*-dibromo complex **1** was shown to react with excess NaBH₄ in ethanol to yield a hydridoborohydride complex **2**. When the amount of NaBH₄ was reduced to 1 equiv with respect to **1**, a hydridobromide complex **3** was obtained as a mixture of *syn* and *anti* isomers (defined by the relationship between NH and FeH hydrogens), which is similar to what Beller et al. observed for the reaction of **1** with NaHBet₃.³⁶ We however found that recrystallization of the isomeric mixture in toluene–pentane at 0 °C led to the isolation of only the *anti* isomer, as confirmed by X-ray crystallography. The solid-state structure also revealed **3** being a dimer linked by N–H···Br hydrogen bonds (Figure S5). Structural analysis of the dibromo complex **1** showed similar H-bonding interactions between two molecules, except

that another molecule was found in the unit cell being H-bonded to a THF solvent molecule (Figure S2).

Complex **2** was first tested as an ester hydrogenation catalyst using methyl benzoate as the substrate. Upon investigating a variety of conditions (Table S2), it was determined that the reaction was best carried out in toluene at 115 °C under 150 psig of H₂ pressure. In the presence of 3 mol % of **2**, a quantitative conversion of methyl benzoate (~1.4 M) to benzyl alcohol was observed within 3 h, as judged by GC and NMR. Complex **3** was also found to be an active catalyst, but 10 mol % of KO^tBu was needed as an additive and the reaction had to be conducted in THF to ensure that KO^tBu was fully dissolved. In addition, despite a high conversion of methyl benzoate, the GC yield for benzyl alcohol was merely 72%.³⁸

Because complex **2** has the advantage of being an active catalyst without an added base and because it leads to higher selectivity for alcohol formation, we decided to focus on **2** for studying the substrate scope of iron-catalyzed ester hydrogenation reactions. As shown in Table 1, aromatic esters **4a–g**

Table 1. Hydrogenation of Esters Catalyzed by **2**^a

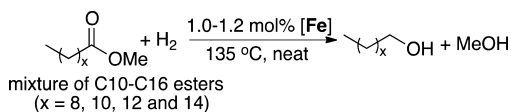


were hydrogenated under 150 psig of H₂ pressure, and the corresponding alcohol products were isolated in high yield. The catalytic system is compatible with functionalities including CF₃, MeO, and Cl groups. Ester **4e**, which contains an electron-donating MeO substituent at the *para* position of the aromatic ring, was shown to react slowly, consistent with the less electrophilic nature of the carbonyl group. The more challenging aliphatic esters **4i–l** were also hydrogenated successfully, albeit requiring a higher H₂ pressure (230 psig) and a longer reaction time. For methyl cinnamate (**4m**), both

C=O and C=C bonds were hydrogenated, leading to a fully saturated alcohol. Hydrogenation of cinnamyl alcohol under the same catalytic conditions gave **5m** in 23% yield (determined by NMR). Interestingly, the reaction of methyl salicylate (**4n**) did not yield any product, perhaps due to the acidic phenol hydrogen.

Having established the catalytic utility of **2** in hydrogenating esters that are commonly investigated in the literature, we shifted our attention to an industrial sample, CE-1270, which is derived from coconut oils and consists of methyl laurate (C12, 73%), methyl myristate (C14, 26%), and a small amount of C10 and C16 methyl esters (~1%).³⁹ In our study, hydrogenation of CE-1270 was carried out under neat conditions, which would simplify separation, and the low boiling byproduct methanol could be readily recycled for the manufacturing of methyl esters from natural oils. At 135 °C under 750 psig of H₂ pressure, when **2** was used as the catalyst (1 mol %), CE-1270 (typically 1.6–1.7 g) was fully converted in 3 h, producing a mixture of fatty alcohols in a combined GC yield of 98.6% (Table 2). Decreasing the hydrogen pressure to 300 psig led to

Table 2. Catalytic Hydrogenation of CE-1270



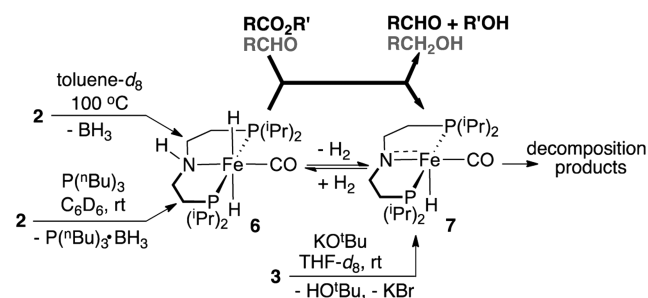
catalyst (mol %)	additive (mol %)	<i>p</i> (H ₂) (psig)	time (h)	alcohol yield (%) ^a
2 (1.0)	none	750	3	98.6
2 (1.0)	none	300	3	72.6
2 (1.2)	none	750	1	96.2
1 (1.0)	NaOMe (2.0)	750	6	0.8
3 (1.1)	NaOMe (2.2)	750	3	52.2 ^b

^aCombined GC yield of all fatty alcohols. ^b23.3% fatty–fatty esters present.

a lower yield of alcohols. The dibromo complex **1** proved to be an inactive catalyst even in the presence of a base. In contrast, hydridobromide complex **3**, when combined with 2 equiv of NaOMe, was found to be catalytically active. However, a significant amount of fatty–fatty or wax esters² was also obtained. In an effort to scale up the hydrogenation process and reduce the catalyst loading, 150 g of CE-1270 were mixed with 0.26 mol % of **3** and heated at 135 °C under 750 psig of H₂ pressure. The combined yield of fatty alcohols reached the maximum of ~25% within 1 h (Table S3 and Figure S6), suggesting that significant catalyst degradation had occurred. A similar hydrogenation reaction carried out at 115 °C extended the catalyst lifetime and improved the maximum alcohol yield to 40%, thus giving a turnover number (TON) of 154 and an initial turnover frequency (TOF) of 137 h⁻¹ (for the first hour).

More detailed mechanistic studies of this catalytic system are in progress. Based on the current understanding of related ruthenium chemistry,^{7,9,12,19} we propose that the real catalytically active species is a *trans*-dihydride complex **6** (Scheme 2). This compound was generated when a solution of **2** in toluene-*d*₈ was heated at 100 °C but quickly converted to **7** as a result of losing H₂. Alternatively, **6** could be produced from **2** at rt through the trapping of BH₃ by P(ⁿBu)₃. Under an argon atmosphere, loss of H₂ from **6** was observed even at rt, and upon standing, the mixture of **6** and **7** eventually decomposed to intractable species. However, under an H₂ (~1 atm)

Scheme 2. Formation, Stability, and Catalytic Role of the *trans*-Hydride Complex



atmosphere, the *in situ* generated **7** (from **3** and KO^tBu) was converted to **6** in >90% yield without much decomposition. Hydrogen transfer from **6** to an ester substrate RCO₂R' could lead to **7**, RCHO, and R'CH₂OH, which may or may not involve a hemiacetal intermediate RCH(OH)OR'. Further reduction of RCHO to RCH₂OH by **6** completes the overall hydrogenation process. How exactly does the hydrogen transfer from **6** occur, and whether or not the reduced product remains coordinated to **7** are beyond the scope of this report, but they are as important as the information on how **6** is initially formed and regenerated and the extent of catalyst decomposition. The catalyst loading, temperature, and hydrogen pressure mentioned earlier for the catalytic studies are likely to be a balance struck among all these factors.

In conclusion, we have reported the first iron-based homogeneous catalysts for the hydrogenation of unactivated esters to alcohols. This catalyst system is not only applicable to a variety of aromatic and aliphatic esters but also amenable to industrial samples and can be performed under neat conditions. In terms of catalytic efficiency, iron catalysts described herein are comparable to many ruthenium catalysts, but not yet as competitive as the most active ruthenium catalysts.^{8,9} Nevertheless, we have demonstrated the viability of using iron catalysts for homogeneous hydrogenation of esters, and more in-depth mechanistic studies are expected to lead to the discovery of more efficient and practical catalysts.

■ ASSOCIATED CONTENT

📄 Supporting Information

Experimental details and crystallographic data for **1**–**3** (CIF and PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Author Contributions

[§]S.C. and H.D. contributed equally.

Notes

Portions of this work have been disclosed in a provisional patent application with a serial number of 61/972927.

The authors declare no competing financial interest.

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- (38) GC-MS shows a small amount of PhCHO (~2%) as the byproduct. We suspect that under basic conditions some of the PhCH₂OH could break down to yield volatiles, as demonstrated by Beller et al. for MeOH.³⁶
- (39) The end-use applications for the corresponding fatty alcohols are surfactants, defoamers, cosmetics, aluminum rolling lubricants, concrete antispalling agents, lubricant oil additives, and plasticizers, to name a few.