Iron Catalysis

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Hydrogenation of Esters to Alcohols with a Well-Defined Iron Complex

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Dedicated to the MPI für Kohlenforschung on the occasion of its centenary

Abstract: *We present the first base-free Fe-catalyzed ester reduction applying molecular hydrogen. Without any additives, a variety of carboxylic acid esters and lactones were hydrogenated with high efficiency. Computations reveal an outer-sphere mechanism involving simultaneous hydrogen transfer from the iron center and the ligand. This assumption is supported by NMR experiments.*

As one of the major redox transformations in organic chemistry, the reduction of esters to alcohols is frequently used in natural product synthesis and for the preparation of organic building blocks. In addition, this methodology is important in industry for the production of agrochemicals and pharmaceuticals, as well as for flavors and fragrances.[1] Reliable procedures for ester reduction make use of stoichiometric amounts of aluminum or boron hydrides, but suffer from high cost, low atom economy, laborious work-up, and safety issues.[2] Compared to these classic stoichiometric reduction processes, catalytic hydrogenations proceed more efficiently and no salt waste is formed. Thus, on bulk scale heterogeneous metal-oxide-based catalysts are applied to hydrogenate fatty acid esters to the corresponding alcohols. Unfortunately, these catalysts operate under drastic conditions (high pressure and temperature).[3,4] Therefore, the development of defined organometallic complexes which work under milder conditions is of increasing interest and offers some potential.

In fact, in the last decades a number of homogeneous catalysts for the hydrogenation of carboxylic acid esters, which are preferentially based on ruthenium, have been developed.[5] Since the early studies by Grey and Pez[6] tremendous progress has been made in this field.[7,8] Significant advances have been achieved by the groups of Saudan,[9b] Milstein,[9a,c-e] and Kuriyama.[10] Notably, all their benchmark catalysts are well-defined ruthenium complexes bearing chelating PN or pincer-type PNP ligands. Recently, Milstein reported a first example for an iron-catalyzed hydrogenation of esters but activation by base is required.[9e]

Based on our long-standing interest in non-noble-metal-catalyzed redox catalysis and our experience in the reduction of carboxylic acid derivatives,[11,12] we became interested in the development of similar hydrogenations using an iron catalyst. The hydrogenation of standard esters, flavor and fragrance compounds, and a pharmaceutical intermediate of Alisporivir proceeded under relatively mild conditions without any additives!

Inspired by recent work on the hydrogenation of carbonyl functionalities with iron pincer complexes,[13] we prepared the

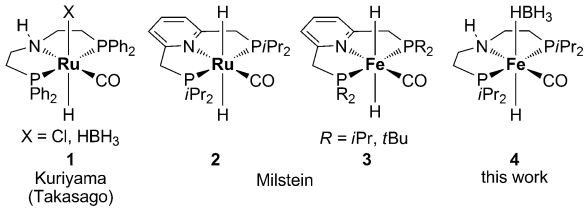

Figure 1. Selection of hydrogenation catalysts **1**–**3** with PNP ligands and our iron complex **4**.

novel, well-defined iron complex **4** at the start of this project (Figure 1).[14,15] For our initial catalytic investigations, we chose the reduction of methyl benzoate in the presence of 1 mol% of catalyst **4** at 50 bar H_2 and 100 °C. To our delight, the desired reaction was complete after 360 min giving a very high yield (93%) of benzyl alcohol (see the Supporting Information). Optimization of key reaction parameters such as temperature, pressure, and catalyst loading showed that the hydrogenation can be also achieved at 60 °C, albeit giving a lower yield of **6a** (Table 1, entries 1–4).

Gratifyingly, decreasing the pressure to 30 bar H_2 led to an excellent product yield of 97% (Table 1, entry 5). Interestingly, even the reaction with 10 bar H_2 gave a good yield (88%) of the desired product (Table 1, entry 6).

At this point it is important to note that for most ruthenium catalysts a substantial amount of base is required to form the catalytically active species. For our iron system no additional base is needed. Nevertheless, we tested the influence of several basic and acidic additives in the model reaction (Figure 2). To observe an effect, not the optimal

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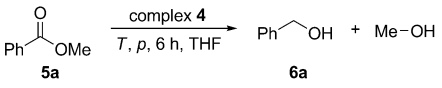
Table 1: Hydrogenation of methyl benzoate: optimization.[a]



5a 6a

Entry	Catalyst loading [mol%]	*T* [°C]	*p* [bar]	Conv. [%][b]	Yield [%][b]
1	1	130	50	>99	93
2	1	100	50	>99	93
3	1	80	50	87	82
4	1	60	50	52	49
5	1	100	30	>99	97
6	1	100	10	91	88
7	1	100	1	43	6
8	0.5	100	30	3	3

[a] Methyl benzoate (0.5 mmol), **4** (0.005 mmol), 1 mL THF, 6 h, *T*. [b] Conversion and yield were determined by GC analysis using hexadecane as an internal standard.

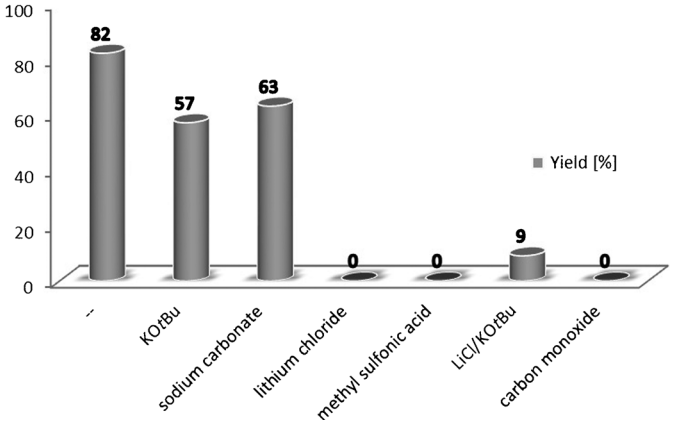
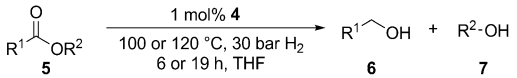


Figure 2. Hydrogenation of methyl benzoate with different additives: methyl benzoate (0.5 mmol), **4** (0.005 mmol), additive (0.05 mmol) or 5 bar CO, 1 mL THF, 6 h, 50 bar H_2, 80 °C. Conversion and yield are determined by GC using hexadecane as an internal standard.

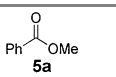
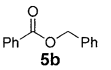
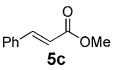
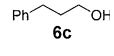
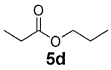
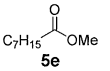
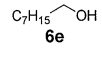
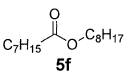
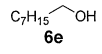
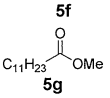
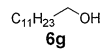
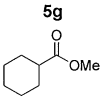
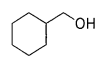
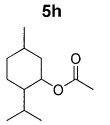
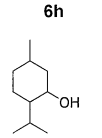
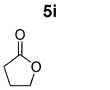
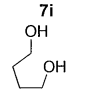
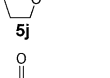
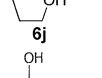
conditions (80 °C, 50 bar H_2) were applied. Surprisingly, lower yields were obtained with 10 mol% of potassium *tert*-butoxylate and sodium carbonate. The addition of lithium chloride or methyl sulfonic acid as well as added carbon monoxide in the applied hydrogen gas inhibited the hydrogenation of methyl benzoate.

To prove the general applicability of the novel catalyst system, different esters and lactones were reduced to the corresponding alcohols/diols using 1 mol% **4** in 1 mL THF at 30 bar H_2 (Table 2). The model substrate with its fruity flavor was hydrogenated to **6a** with an excellent yield of 97% (Table 2, entry 1). Excellent yield and conversion was obtained for methyl cinnamate (**5c**), giving 3-phenyl-1-propanol (**6c**) (Table 2, entry 3). Short- and long-chain, aliphatic linear compounds such as propyl propanoate, methyl octanoate, octyl octanoate, and methyl laurate were reduced towards the corresponding alcohols with yields between 67 and 97% (Table 2, entries 4–7). However, the hydrogenation of methyl cyclohexanecarboxylate gave a high yield of 92% (Table 2, entry 8). Hydrogenation of menthyl

Table 2: Iron-catalyzed hydrogenation of various aromatic and aliphatic esters as well as lactones: flavors and fragrances.[a]



5 6 7

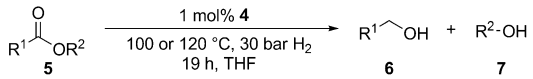
Entry	Ester	Alcohol	*T* [°C]	*t* [h]	Yield[b] [%]
1	 5a	 6a	100	6	97
2	 5b	 6a	120	19	86[c]
3	 5c	 6c	100	6	99
4	 5d	 6d	120	19	68[c]
5	 5e	 6e	120	19	97
6	 5f	 6e	120	19	67[c]
7[d]	 5g	 6g	120	19	97
8[e]	 5h	 6h	120	19	92
9[d,f]	 5i	 7i	120	19	50
10	 5j	 6j	120	19	89
11[d]	 5k	 6k	120	19	69[g]

[a] Substrate (0.5 mmol), **4** (0.005 mmol), 1 mL THF, 30 bar H_2, 6 or 19 h, 100 or 120 °C. [b] Yield determined by GC using hexadecane as an internal standard. [c] Alcohol **6** = **7**, was taken into account for yield determination. [d] **4** (0.01 mmol). [e] **5h** (2 mmol), **4** (0.025 mmol), 4 mL THF, 50 bar H_2, 19 h, 120 °C, 25 mL autoclave. [f] In addition, the hydrogenation of L-menthyl acetate (>97% enantiomeric purity) to L-menthol resulted in 0% loss of chiral information. [g] Yield of isolated product.

acetate (**5i**) led to ethanol and menthol (**7i**, 50%). Additionally, two lactones were transformed into the corresponding diols with good to high yields of 69–89% (Table 2, **6j** and **k**).

As shown in Table 3 (entry 1) also sterically hindered esters can be hydrogenated in excellent yield. Hence, isopropyl benzoate (**5l**) was reduced to **6l** in 96%. High yields were observed for the reduction of methyl 3,4-dimethyl benzoate as well as for methyl-4-methoxy benzoate towards the corresponding alcohols (Table 3, entries 2 and 3). Besides the successful reduction of a diester to the diol (Table 3, entry 4), ethyl cyclobutylcarboxylate led to a respectable yield of 86% (Table 3, entry 7). Interestingly, when the

Table 3: Additional substrates.[a]



5 6 7

Entry	Ester	Alcohol	T [°C]	Yield[b] [%]
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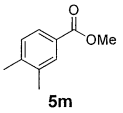
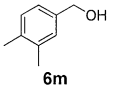
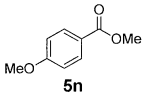
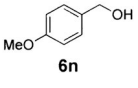
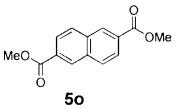
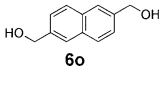
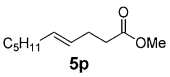
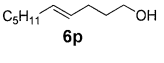
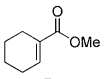
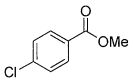
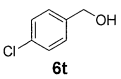
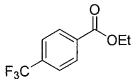
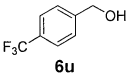
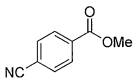
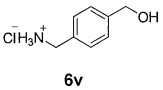
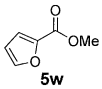
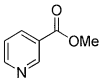
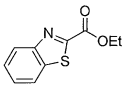
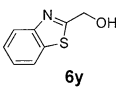
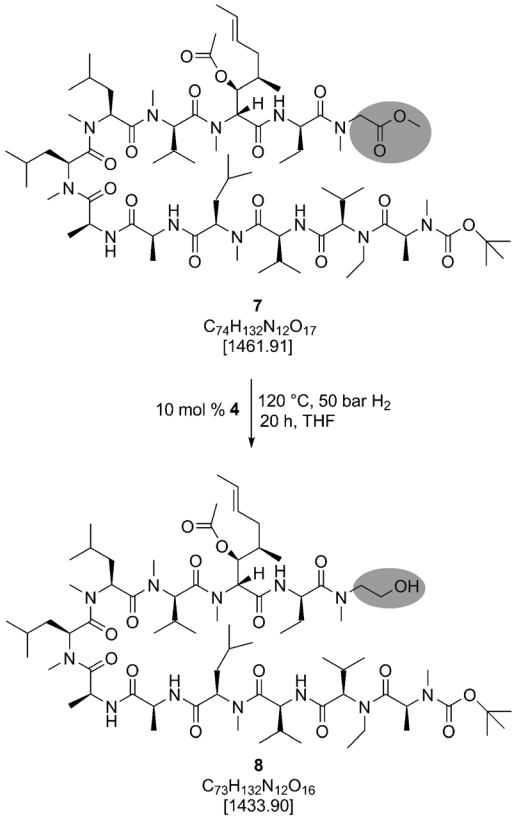
2	 5m	 6m	100	87
3	 5n	 6n	100	87
4	 5o	 6o	100	49
5	 5p	 6p	120	99[c]
6[d]	 5q	 6q	120	85
7	 5r	 6r	120	86
8	 5s	 6s	100	71
9[e]	 5t	 6t	120	85
10[e]	 5u	 6u	120	62
11[f]	 5v	 6v	120	86[g]
12[f]	 5w	 6w	120	90
13[f]	 5x	 6x	120	81
14[d]	 5y	 6y	120	63

[a] Substrate (0.5 mmol), **4** (0.005 mmol), 1 mL THF, 30 bar H_2, 19 h, 100 or 120 °C. [b] Yield determined by GC using hexadecane as an internal standard. [c] *cis*-4-Decen-1-ol was used for product calibration. [d] **4** (0.025 mmol). [e] 0.025 mmol **4**, 50 bar H_2. [f] Substrate (2 mmol), **4** (0.025 mmol), 4 mL THF, 50 bar H_2, 19 h, 120 °C, 25 mL autoclave. [g] Yield of isolated HCl salt.

aliphatic unsaturated ester **5p** was used, no reduction of the double bond was observed (Table 3, entry 5). In addition, phthalide **5s** gave the desired diol in 71% yield (Table 3, entry 7). Gratifyingly, when we evaluated the functional group tolerance, moderate to good results were obtained for halogen, nitrile, and heteroaromatic systems (Table 3, entries 9–14). Furthermore, also methyl 2-bromobenzoate was hydrogenated with a low yield of 21% (5 mol% of **4**).

To highlight this first base-free iron-catalyzed hydrogenation of esters, we focused our attention on a highly challenging substrate of practical importance (Scheme 1). Dodeca-



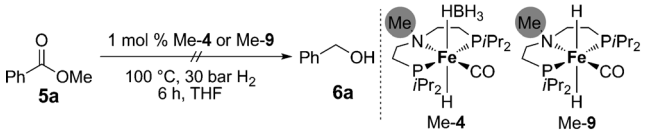
Scheme 1. Hydrogenation of dodecapeptide **7** to **8**.

peptide **7** is an intermediate in the synthesis of Alisporivir, which is used for the treatment of inflammatory and viral diseases.[16] A key step for the cyclization of **7** to Alisporivir involves the reduction of the ester group to the corresponding alcohol, which is achieved on an industrial scale with an excess of sodium borohydride.[17] The major synthetic challenge of the transformation relies on fine-tuning the reactivity of the system to selectively reduce the terminal methyl ester in the presence of a sensitive acetate. To our delight, when catalyst **4** was used the desired alcohol was isolated in high yield (79%) and with excellent selectivity![18]

Finally, to gain more insight into the mechanism of the iron-catalyzed hydrogenation process, we carried out B3PW91 density functional theory computation, where we have used methyl benzoate and methyl acetate for both aromatic and aliphatic esters. All computational details are

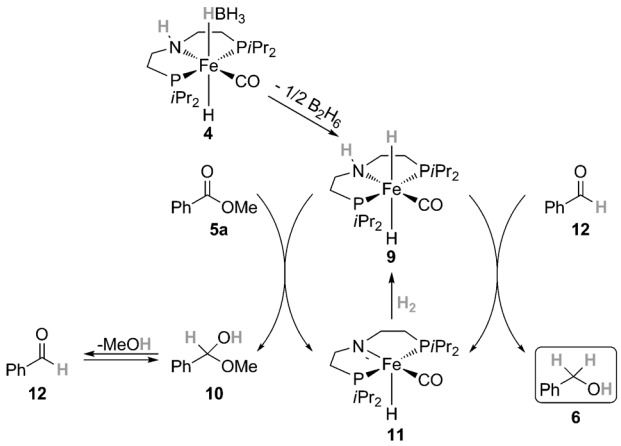
given in the Supporting Information and only the essential results are discussed and compared here. In our previous study on the hydrogenation of nitriles to amines by using catalyst **4**, we identified an outer-sphere mechanism by a simultaneous transfer of the hydride from the iron center and the proton from the nitrogen to the nitrile to give the corresponding imine, based on experimental and computational analyses.[14b] The most important feature in this reaction is the reversible process between the hydrogenation and dehydrogenation of catalyst **9** and its amido intermediate **11**. The barrier for the addition of hydrogen to **11** to give **9** is 17.14 kcal mol^{-1} and the reaction is slightly exergonic by 0.33 kcal mol^{-1}. For the formation of the hemiacetal, the computed free energy barrier of methyl benzoate and methyl acetate is 21.51 and 22.98 kcal mol^{-1}, respectively. However, this reaction step is endergonic by 11.93 and 10.61 kcal mol^{-1}, respectively. For the dissociation of the hemiacetal to the corresponding aldehyde and methanol, the reaction is exergonic by 8.21 and 4.05 kcal mol^{-1} for methoxy(phenyl)-methanol and 1-methoxyethanol, respectively. The hydrogenation of benzaldehyde to benzyl alcohol has a free energy barrier of 6.60 kcal mol^{-1} and is exergonic by 3.30 kcal mol^{-1}. In contrast, the activation of acetaldehyde to ethanol is barrierless and exergonic by 6.49 kcal mol^{-1}. Such small differences in free energy connecting aldehyde and alcohol reveal the reversibility between hydrogenation and dehydrogenation when the reaction conditions are changedby changing the reaction conditions. Noteworthy, the first step of the hemiacetal formation is the rate-determining step on the whole potential surface. In order to support the assumption of an outer-sphere mechanism, which is based on the critical role of the N-H group of the PNHP*i*Pr ligand, iron(II) complexes analogous to **4** and **9** (Me-**4** and Me-**9**) were prepared. Me-**4** and Me-**9**, containing the ligand PNMeP*i*Pr (PNMeP*i*Pr = bis[(2-diisopropylphosphino)ethyl]methyl amine), where the hydrogen of the central nitrogen of the pincer ligand is replaced by a methyl group, should not be active.[19]

As expected, no conversion of methyl benzoate under the standard conditions described in Table 2 was achieved with either of the two iron complexes (Scheme 2).This demonstrates clearly that a cooperative interaction involving the N-H unit of the pincer ligand and the Fe-H group is required for catalytic hydrogenation.



Scheme 2. Hydrogenation of methyl benzoate with complexes Me-**4** and Me-**9**.

Based on these results we propose the following mechanism for the hydrogenation of methyl benzoate (**5a**) (Scheme 3). The ester is hydrogenated in a concerted way by the simultaneous transfer of the hydride from the iron center and the proton from the nitrogen ligand in complex **9** to give the corresponding hemiacetal **10** and amido complex **11**. Next, the dissociation of hemiacetal **10** to benzaldehyde (**12**) and methanol takes place, while **9** is regenerated from **11** by addition of H_2. In the final step, benzaldehyde (**12**) is hydrogenated to give benzyl alcohol **6**.[20]



Scheme 3. Proposed mechanism for the Fe-catalyzed ester hydrogenation: Methyl benzoate (**5a**) serves as a representative example.

In summary, the first base-free iron-based catalyst system for the hydrogenation of various carboxylic acid esters and lactones was developed and showed high efficiency. The practical importance of the new catalyst system is demonstrated in the challenging reduction of the pharmaceutical intermediate **7**. Based on computations, an outer-sphere mechanism is proposed involving simultaneous hydrogen transfer from the iron center and the ligand.

Experimental Section

Unless otherwise stated, all catalytic hydrogenation experiments using molecular hydrogen were carried out in a Parr Instruments autoclave (300 mL).

Representative experiment: Under an argon atmosphere, a vial was charged with **4** (0.005 or 0.025 mmol), which was dissolved in 1 mL of anhydrous THF. The yellow solution was stirred slowly for 3–5 min before the ester (0.5 mmol) was added. The vial was placed in the alloy plate, which was then placed into the autoclave. Once sealed, the autoclave was purged three times with hydrogen, then pressurized to 30 bar, and heated at 100 °C or 120 °C for 6, 19, or 20 h. Afterwards, the autoclave was cooled to room temperature and depressurized, and the reaction mixture was analyzed by GC or as an isolated product (column chromatography: *n*-pentane/ethyl acetate 2:1) by NMR spectroscopy, GCMS, and HRMS.

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[19] See the Supporting Information.
[20] For the evidence of compound **9** and **11**, see reference [14b].

