Unprecedented Iron-Catalyzed Ester Hydrogenation. Mild, Selective, and Efficient Hydrogenation of Trifluoroacetic Esters to Alcohols Catalyzed by an Iron Pincer Complex**

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Dedicated to Professor Helmut Werner on the occasion of his 80th birthday

Abstract: *The synthetically important, environmentally benign hydrogenation of esters to alcohols has been accomplished in recent years only with precious-metal-based catalysts. Here we present the first iron-catalyzed hydrogenation of esters to the corresponding alcohols, proceeding selectively and efficiently in the presence of an iron pincer catalyst under remarkably mild conditions.*

The reduction of esters to alcohols is an important reaction in organic chemistry.[1] This transformation traditionally involves the use of stoichiometric amounts of metal hydride reagents, such as $LiAlH_4$, $NaBH_4$, and their derivatives. However, these reagents have poor compatibility with functional groups and poor atom economy as a result of the generation of stoichiometric amounts of waste. The catalytic hydrogenation of esters to alcohols is, in contrast, an environmentally benign, waste-free and atom-economical process, which is used industrially on a large scale with fatty esters under harsh conditions employing heterogeneous catalysts. We[2] and others[3–5] have developed homogenous catalysts for the hydrogenation of esters to alcohols. In 2006 we reported the mild, low-pressure hydrogenation of non-activated aromatic and aliphatic ester catalyzed by the Ru pincer complex [(PNN*)Ru(H)(CO)]   (PNN = (2-(di-*tert*-butylphosphino-methyl)-6-diethylaminomethyl)pyridine));   the   asterisk denotes the dearomatized ligand).[2a] Based on stoichiometric experiments, we suggested a mechanism that involves a new type of metal–ligand cooperation,[6] which is based on the aromatization/dearomatization of the pyridine-based pincer-type ligand by protonation/deprotonation of the pyridinyl-methylenic carbon atom. 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. These bifunctional

catalysts either employ metal–ligand cooperation by aromatization/dearomatization or a Noyori–Ikariya-type metal NH bifunctional effect. However, most catalysts still require high pressures and high catalyst loadings for an efficient reaction.

The Ikariya group recently reported the hydrogenation of α-fluorinated esters using the Ru pincer complex [(dpa)-Ru(H)(CO)(Cl)]   (dpa = bis-(2-diphenylphosphinoethyl)-amine) as catalyst.[3g] These reactions give, depending on the reaction conditions, α-fluorinated alcohols or hemiacetals. Shortly after, the same catalyst was used for hydrogenation reactions of perfluoro methyl esters by Lazzari, Cassani, and co-workers.[3n] Similar and remarkably efficient Ru catalysts featuring NH-functionalized pincer ligands were recently developed by Gusev and co-workers.[3p]

The substitution of expensive and potentially toxic noble-metal catalysts by inexpensive, abundant, and environmentally benign metals is a prime goal in chemistry. In particular, iron is an attractive alternative because of its high abundance, low cost, and low toxicity. In recent reports, there is a remarkable progress in the application of iron-based catalysts for hydrogenation, dehydrogenation, and transfer-hydrogenation reactions.[7] Iron catalysts have been successfully applied in hydrogenation reactions of various substrates, such as alkynes,[8] alkenes,[8b, 9] ketones,[10] aldehydes,[10e, 11] imines,[10f, 12] and CO_2.[13] However, although catalysts for the hydrogenation of esters based on non-noble metals are highly desirable, so far only Ru,[2, 3] Ir,[4] and Os[5]-based catalysts have been reported. Moreover, many iron-based hydrogenation catalysts, such as Knölker-type catalysts, bis(iminopyridine)–iron catalysts, or Beller's dual iron catalyst for the hydrogenation of α-keto- and α-iminoesters to α-hydroxy- and α-aminoesters, respectively, are tolerant toward esters.[14] However, two-step strategies of iron-catalyzed ester reductions to alcohols,[15] aldehydes,[16] and ethers[17] through hydrosilylation followed by acidic or basic workup were developed, although they are not atom-economical.

Encouraged by the recent developments of iron pincer complexes as catalysts for hydrogenation and dehydrogenation reactions in our group,[8c, 10c,d, 13b, 18] we investigated their application as catalysts for the hydrogenation of fluorinated esters. To our knowledge, no iron-catalyzed hydrogenation reaction of esters or other carboxylic acid derivatives was reported to date. Herein, we present an efficient and selective method for the hydrogenation of trifluoroacetic esters to the corresponding alcohols catalyzed by the iron pincer complex

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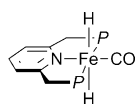
Scheme 1. Catalyst 1 (P = PtBu₂).

trans-[(*t*Bu-PNP)Fe(H)₂(CO)] (**1**, *t*Bu-PNP = 2,6-bis(di-*tert*-butylphosphinomethyl)pyridine, Scheme 1).

Complex **1** efficiently catalyzes the hydrogenation of 2,2,2-trifluoroethyl trifluoroacetate to 2,2,2-trifluoroethanol (TFE) under remarkably mild conditions (Table 1). Initially

Table 1: Hydrogenation of 2,2,2-trifluoroethyl trifluoroacetate to 2,2,2-trifluoroethanol (TFE) catalyzed by iron pincer complex **1**.[a]

Entry	**1** [mol %]	KOtBu [mol %]	p(H₂) [bar]	t [h]	T [°C]	Yield [%]
1	0.50	0	10	16	40	2
2	0.50	1.0	10	16	40	>99
3	0.50	1.0	10	1	40	85
4	0.50	1.0	10	2	40	98
5	0	1.0	10	16	40	1
6	0.25	1.0	10	16	40	74
7	0.05	1.0	10	90	40	64
8	0.50	1.0	10	16	24	91
9	0.50	1.0	5	16	40	94
10[b]	0.50	1.0	10	16	40	>99
11[c]	0.50	1.0	10	2	40	99

[a] Reaction conditions: ester (2.0 mmol), 1,4-dioxane (2 mL), performed in a Fisher–Porter pressure vessel. Yields based on integration of ¹⁹F{¹H} NMR spectra of the crude products. [b] Performed in the presence of 0.9 g Hg. [c] Performed in the presence of PMe₃ (0.15 mol% with respect to **1**).

the *trans*-dihydride complex **1** was investigated as a catalyst for the hydrogenation of 2,2,2-trifluoroethyl trifluoroacetate under base-free conditions. A reaction performed in a Fisher–Porter pressure vessel with a hydrogen pressure of 10 bar and a catalyst loading of 0.50 mol% in 1,4-dioxane as solvent leads to the formation of TFE in an unsatisfactory yield of 2%, according to integration in the ¹⁹F{¹H} NMR spectrum of the crude product (Table 1, entry 1). The activity of the catalyst increases significantly upon the addition of base. The same reaction leads to full conversion to TFE in the presence of 1.0 mol% of KOtBu after 16 h at 40°C (Table 1, entry 2), giving yields of 85% and 98% after 1 h and 2 h, respectively (Table 1, entries 3 and 4). This corresponds to a turnover frequency (TOF) of 170 h⁻¹ for the first hour. No catalytic conversion to TFE was observed in the absence of catalyst **1** (Table 1, entry 5).[19] When the same reaction was conducted with half of the catalyst loading (0.25 mol%), a yield of 74% was obtained after 16 h (Table 1, entry 6). Further reducing the catalyst loading to 0.05 mol% resulted in a 64% yield after a reaction time of 90 h (Table 1, entry 7), which corresponds to a turnover number (TON) of 1280. The catalytic system shows a significant activity even at ambient temperature. A reaction with 0.50 mol% of **1** and 1.0 mol% of KOtBu at 24°C (± 1°C) gave a comparatively good yield of 91% (Table 1, entry 8). Furthermore, the catalysis was performed at even lower pressures of hydrogen. Reducing the pressure to 5 bar gave TFE in 94% yield after 16 h with

a catalyst loading of 0.50 mol% of **1** and a KOtBu loading of 1.0 mol% (Table 1, entry 9). No poisoning of the catalyst was observed in the presence of mercury (Table 1, entry 10) or PMe₃ (30% with respect to **1**, entry 11), this indicates that catalysis by nanoparticles is unlikely.[20]

Treatment of TFE with 2.0 mol% of complex **1** and 10 mol% of KOtBu at 40°C and 100°C did not show any reaction of the alcohol to a dehydrogenation product, such as the corresponding aldehyde, hemiacetal, or ester after 24 h. These results suggest that the hydrogenation reaction is irreversible under these conditions.

Catalyst **1** is less active for the hydrogenation of *n*-butyl trifluoroacetate to TFE and *n*-butanol (Table 2). Experiments at different temperatures were conducted using 10 bar of

Table 2: Hydrogenation of *n*-butyl trifluoroacetate to 2,2,2-trifluoroethanol (TFE) and *n*-butanol catalyzed by iron pincer complex **1**.[a]

Entry	Base ([mol %])	Solvent	t [h]	T [°C]	Yield [%]
1	KOtBu (4.0)	1,4-dioxane	16	24	30
2	KOtBu (4.0)	1,4-dioxane	16	40	48
3	KOtBu (4.0)	1,4-dioxane	16	70	25
4	KOtBu (4.0)	1,4-dioxane	16	100	16
5	KOtBu (2.0)	1,4-dioxane	16	40	32
6	KOtBu (10)	1,4-dioxane	16	40	55
7	KOtBu (2.0)	1,4-dioxane	66	40	31
8	KOtBu (4.0)	1,4-dioxane	66	40	57
9	KOtBu (10)	1,4-dioxane	66	40	66
10	KH (10)	1,4-dioxane	16	40	52
11	KOH (10)	1,4-dioxane	16	40	1
12	NaOMe (10)	1,4-dioxane	16	40	68
13	NaOEt (10)	1,4-dioxane	16	40	59
14	NaO*i*Pr (10)	1,4-dioxane	16	40	59
15	NaOMe (10)	THF	16	40	69
16	NaOMe (10)	toluene	16	40	46
17	NaOMe (10)	MeOH	16	40	1

[a] Reaction conditions: H₂ (10 bar), ester (1.0 mmol), **1** (2.0 mol%), 1,4-dioxane (2 mL), base, performed in a Fisher–Porter pressure vessel. Yields based on integration of the ¹⁹F{¹H} NMR spectra of the crude products.

hydrogen pressure, 2.0 mol% of catalyst **1**, and 4.0 mol% of KOtBu, and the yields of TFE were compared after 16 h (Table 2, entries 1–4). The highest activity of **1** in the hydrogenation reaction was observed at 40°C (Table 2, entry 2), resulting in a yield of 48%. Experiments performed at higher or lower temperatures resulted in lower yields (Table 2, entries 1, 3, and 4). We studied the effect of different KOtBu concentrations on the reaction. Lowering the KOtBu loading to 2.0 mol% resulted in a deceleration of the reaction (Table 2, entries 5 and 7), whereas an increase of the KOtBu loading to 10 mol% (Table 2, entries 6 and 9) gave the products in higher yields.

Next, we applied 10 mol% of different bases in reactions with 2.0 mol% of catalyst **1** and compared the yields after 16 h at 40°C (Table 2, entries 6 and 10–14). These experiments showed that the activity of the catalytic system depends

on the base. KH and alkoxide bases are suitable bases for the reaction, whereas the use of KOH gives an unsatisfying yield. An increase in activity was observed in the series KOH (TON = 0.5), KH (TON = 26), KOtBu (TON = 27.5), NaOiPr (TON = 29.5), NaOEt (TON = 29.5), and NaOMe (TON = 34). Additionally, the effect of various solvents on the reaction was examined (Table 2, entries 12 and 15–17). A series of reactions was performed using 2.0 mol% of **1** and 10 mol% of NaOMe under 10 bar of H_2 pressure, and the yields were determined after 16 h at 40°C. The use of 1,4-dioxane and THF as solvents gave practically the same yields (68% and 69%, respectively), whereas the reaction in toluene resulted in a slightly lower yield of 46%. Using MeOH as solvent resulted in the deactivation of the catalyst, and TFE was obtained in only 1% yield after 16 h.

The catalytic activity of catalyst **1** increased with higher pressures of H_2. A reaction with half the catalyst loading (1.0 mol%) and half the amount of NaOMe (5.0 mol%) gave TFE in 77% yield after 16 h with a H_2 pressure of 25 bar (Table 3, entry 1). Various trifluoroacetic esters were smoothly hydrogenated under these mild conditions (Table 3). Aliphatic, olefinic, and aromatic esters were reduced with good to excellent yields and selectivity. Notably, other functional groups, such as ethers (Table 3, entry 2), aryl groups (entry 3, 7–10), and terminal (entry 5) and internal (entry 6) C=C bonds stayed intact during the catalytic hydrogenation.

The reaction proceeded more slowly for substrates with bulky substituents at the ester alkoxy group, such as cyclohexylmethyl trifluoroacetate (substituted at the β-carbon atom; Table 3, entries 11 and 12) and isopropyl trifluoroacetate (substituted at the α-carbon atom; Table 3, entries 13 and 14). However, high yields were obtained after prolonged reaction times. The same effect, a decrease in reaction rate for substrates with an increasing steric demand on the ester oxygen atom, was described very recently by Morris in a comprehensive study.[3g] Notably, no catalytic hydrogenation was observed for esters bearing only two fluoro substituents at the methyl carbon atom of the acetate moiety. Reactions of ethyl chlorodifluoroacetate, ethyl bromodifluoroacetate, and ethyl difluoroacetate did not show any conversion to the corresponding difluoroethanol using 2.0 mol% of **1**, 10 mol% of NaOMe, and 10 bar of H_2 pressure at 40°C after 16 h. Similarly, under the same conditions, no formation of corresponding nonfluorinated alcohol was observed for the reaction of 2,2,2-trifluoroethyl acetate and 1,1,1,3,3,3-hexafluoroisopropyl benzoate.

In order to gain mechanistic understanding of the iron-catalyzed hydrogenation of trifluoroacetates, complex **1** was investigated in stoichiometric reactions (see the Supporting Information). No reaction was observed between complex **1** and an excess amount of KOtBu, suggesting that a dearomatized anionic iron dihydride complex is not involved. Significantly, when the reaction of **1** with approximately 1.5 equivalents of benzyl trifluoroacetate was performed in CD$_3$CN at room temperature, transfer of one hydride of **1** to the ester gave the monocationic acetonitrile complex [(tBu-PNP)Fe(H)(CO)(MeCN)]⁺ (**2**).[21]

Table 3: Hydrogenation of various esters to the corresponding alcohols catalyzed by iron pincer complex **1**.[a]

Entry	Ester	Yield [%]
1		77
2		80
3		78
4		>99
5		95
6		84
7		>99
8		>99
9		>99
10		97
11		52
12[b]		95
13		25
14[c]		77

[a] Reaction conditions: H_2 (25 bar), ester (2.0 mmol), **1** (1.0 mol%), NaOMe (5.0 mol%), 1,4-dioxane (2 mL), 16 h, 40°C, performed in an autoclave. Yields based on integration of the $^{19}F\{^1H\}$ NMR spectra of the crude products. [b] 48 h. [c] Ester (0.67 mmol), **1** (3.0 mol%), NaOMe (15.0 mol%), 60 h.

On the basis of the reactivity of complex **1** and precedents regarding the non-innocent nature of the ligand,[6] a possible bifunctional mechanism for the hydrogenation of trifluoroacetates catalyzed by complex **1** is presented in Scheme 2.[22] We recently reported on the direct attack of CO_2 on the Fe hydride moiety of **1**, forming the oxygen-bound formate complex ([(tBu-PNP)Fe(H)(CO)(η^1-OOCH)] (**3**),[13b] and we showed by DFT calculations that this reversible reaction proceeds through an outer-sphere mechanism.[18c] As shown in Scheme 2, a direct attack of the carbonyl carbon atom of
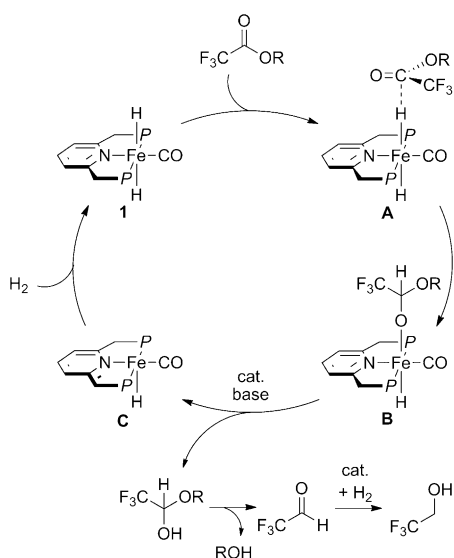
Scheme 2. Possible mechanism of the iron-catalyzed hydrogenation of trifluoroacetate esters ($P = PtBu_2$).

the ester on the Fe hydride moiety of **1** is also observed in the case of the trifluoroacetate ester. This reaction likely proceeds via intermediate **A**, leading to oxygen-bound hemiacetaloxide intermediate **B** (which in acetonitrile forms complex **2**). The OH elimination of the hemiacetal through metal–ligand cooperation generates the dearomatized intermediate **C**. This step, the formation of the deprotonated intermediate **C**, may be facilitated by the presence of a catalytic amount of base.

The dihydride complex **1** is regenerated by addition of H_2 through metal–ligand cooperation. This behavior was previously observed experimentally for dearomatized complexes, such as the Ru complex [(PNN*)Ru(H)(CO)].[2a] The hemiacetal is in equilibrium with the trifluoroacetaldehyde, which is likely to be readily hydrogenated through a similar cycle to give TFE. The outer-sphere nucleophilic attack of the hydride on the ester is obviously facilitated by the electron-deficient character of the carbonyl carbon atom in the trifluoroacetates, and is also in line with the lack of reactivity of the non-polarized C=C bonds (Table 3, entries 5 and 6).

In conclusion, we have demonstrated the catalytic hydrogenation of a family of esters to alcohols without the use of precious or toxic metals as catalysts. Thus, the iron pincer complex [(tBu-PNP)Fe(H)$_2$(CO)] (**1**) is an efficient catalyst for the selective hydrogenation of trifluoroacetic esters to the corresponding alcohols. These reactions proceed smoothly under remarkably mild conditions (5–25 bar and 40°C) to give the products in good to quantitative yields. Further studies on the scope and mechanism of Fe-catalyzed ester hydrogenation are in progress.

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[19] Minor amounts of side products from transesterification with the base were observed occasionally in the hydrogenation reactions (for details, see the Supporting Information).

[20] See, for example: J. F. Sonnenberg, N. Coombs, P. A. Dube, R. H. Morris, *J. Am. Chem. Soc.* **2012**, *134*, 5893–5899.

[21] Complex **2** was reported previously, see Ref. [18c]. Benzyl alcohol was also formed, but the fate of the trifluoroacetyl group of the ester is unclear (for details, see the Supporting Information).

[22] Recently, an alternative mechanism for the hydrogenation of esters with [(PNN*)Ru(H)(CO)] was proposed: F. Hasanayn, A. Baroudi, *Organometallics* **2013**, *32*, 2493–2496.