

# Expanding the catalytic scope of (cyclopentadienone)iron complexes to the hydrogenation of activated esters to alcohols

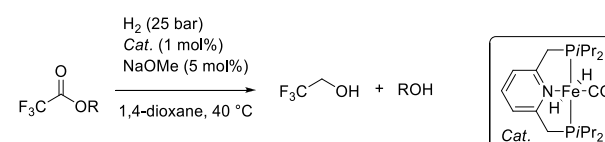
Piotr Gajewski,<sup>[a,b]</sup> Angela Gonzalez-de-Castro,<sup>[b]</sup> Marc Renom-Carrasco,<sup>[a,b]</sup> Umberto Piarulli,<sup>[c]</sup> Cesare Gennari,<sup>[a]</sup> Johannes G. de Vries,<sup>[d]</sup> Laurent Lefort,<sup>[b]\*</sup> and Luca Pignataro<sup>[a]\*</sup>

**Abstract:** Herein, we report the application of the easy-to-make and bench-stable (cyclopentadienone)iron complexes (such as **1**) as pre-catalysts for the hydrogenation of esters. After optimization of the reaction conditions (solvent, temperature, pressure), complex **1** was tested in the hydrogenation of a range of esters. With most of the activated trifluoroacetate esters, a quantitative formation of TFE was obtained at low catalyst loadings. For non-activated esters, no reaction was observed. Trifluoroacetic acid, a common impurity in hydrolytically labile trifluoroacetate esters, was shown to act as a poison for the catalyst. However, the simple addition of Et<sub>3</sub>N allowed to restore the catalyst activity. Our study constitutes the first example of ester hydrogenation with an Fe complex based on a non-pincer ligand.

Catalytic hydrogenations (CHs) are a reaction class of key importance in the sustainable manufacture of both bulk commodities and fine chemicals for several reasons. Firstly, H<sub>2</sub> is a cheap and clean reductant, which allows to achieve a perfect atom economy and to minimize the generation of waste. Secondly, CHs are operationally simple and generally require minimal workup operations for the isolation of the product. Last but not least, as CHs are a very mature research field, countless heterogeneous<sup>[1]</sup> and homogeneous<sup>[2]</sup> catalysts have been developed, which allow to carry out these reactions with high chemo-, regio- and/or stereoselectivity. However, most of these catalysts rely on precious metals (e.g., Ru, Rh, Ir, Pd, Pt), with associated problems of toxicity, high cost and limited stock which prevent, in some cases, their industrial use. Therefore, replacing precious metals with cheap base metals such as Fe, Co or Ni is currently considered a task of primary scientific and industrial relevance.<sup>[3]</sup> From the point of view of sustainability, Fe is certainly the most appealing of these metals, owing to its wide

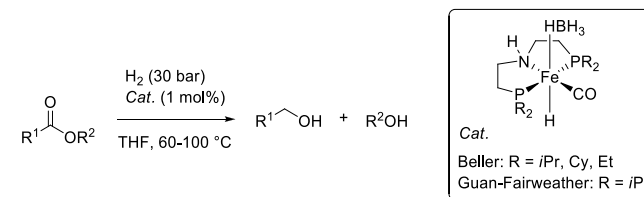
availability (2<sup>nd</sup> most abundant metal in the Earth's crust), low cost and scarce toxicity.<sup>[4]</sup> Accordingly, numerous Fe-based catalysts have been developed in the last decade for the hydrogenation of olefins,<sup>[5]</sup> ketones,<sup>[6]</sup> imines,<sup>[6c,7]</sup> and carbon dioxide/sodium bicarbonate,<sup>[7a, 8]</sup> including several enantioselective versions.<sup>[6i-m,7e,f]</sup> The more difficult ester hydrogenation<sup>[9]</sup> was only recently reported for the first time by Milstein and co-workers (Figure 1 A).<sup>[10]</sup>

## A. Milstein and co-workers<sup>[10]</sup>

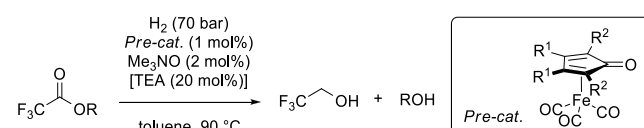


## B. Beller and co-workers<sup>[11]</sup>

### Guan-Fairweather and co-workers<sup>[12]</sup>



## C. This paper



**Figure 1.** Previous examples of Fe-catalyzed ester hydrogenation (A, B), and the new methodology described in this paper (C).

Shortly after the Milstein's report, other examples of Fe-catalyzed ester hydrogenation were described by the groups of Beller<sup>[11]</sup> and Guan-Fairweather<sup>[12]</sup> (Figure 1 B), expanding the substrate scope to non-trifluoroacetate esters.<sup>[13]</sup> However, all these methodologies rely on costly and air-sensitive PNP pincer ligand Fe-complexes,<sup>[10-12]</sup> which hampers their possible industrial use. In sharp contrast, (cyclopentadienone)iron complexes<sup>[14]</sup> (Figure 1 C, Figure 2) are ideal pre-catalysts for industrial applications, as they are easy-to-make and stable compounds.<sup>[15]</sup> Under suitable experimental conditions, these complexes can be converted in situ into catalysts for the hydrogenation of ketones,<sup>[6g,h,k-m]</sup> imines<sup>[7a-d]</sup> and carbon dioxide/sodium bicarbonate.<sup>[7a,8a]</sup> However, to the best of our knowledge, no application of (cyclopentadienone)iron complexes in ester CH has been reported so far.

Building on our expertise in the synthesis and catalytic use of (cyclopentadienone)iron complexes,<sup>[6k,l]</sup> we set to investigate whether they could be employed as pre-catalysts for the hydrogenation of esters. Thus, the "classical" complex **1** (Figure

[a] P. Gajewski, M. Renom-Carrasco, Dr. L. Pignataro, Prof. Dr. C. Gennari

Università degli Studi di Milano, Dipartimento di Chimica  
Via C. Golgi, 19, I-20133, Milan (Italy)

[b] P. Gajewski, Dr. A. Gonzalez-de-Castro, M. Renom-Carrasco, Dr. L. Lefort

DSM Innovative Synthesis BV,  
P.O. box 18, 6160 MD Geleen (The Netherlands)  
E-mail: laurent.lefort@dsm.com

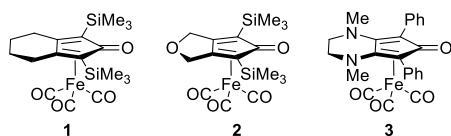
[c] Prof. Dr. U. Piarulli

Università degli Studi dell'Insubria,  
Dipartimento di Scienza e Alta Tecnologia,  
Via Valleggio, 11, I-22100, Como (Italy)  
E-mail: umberto.piarulli@uninsubria.it

[d] Prof. Dr. J. G. de Vries

Leibniz-Institut für Katalyse e. V.  
Albert-Einstein-Str., 29 a 18059 Rostock (Germany)

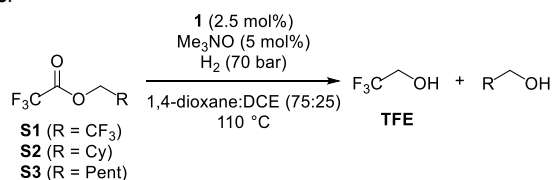
2) was tested, after in situ activation with Me<sub>3</sub>NO,<sup>[6i-m,7a-d]</sup> in the hydrogenation of activated trifluoroacetate substrates **S1-S3** (Table 1). The first experiments were carried out under 70 bar of H<sub>2</sub> at 110 °C for 17 h.



**Figure 2.** Examples of (cyclopentadienone)iron complex.

As in the Fe-catalyzed hydrogenation of **S1** reported by Milstein and co-workers,<sup>[10]</sup> we intended to use 1,4-dioxane as solvent. However, Me<sub>3</sub>NO – i.e. the catalyst activator – was poorly soluble in 1,4-dioxane. Therefore, it was added to the catalytic mixture from a 1,2-dichloroethane (DCE) stock solution. Consequently our initial trials were done using a 1,4-dioxane/DCE solvent mixture.

**Table 1.** Test of pre-catalyst **1** in the hydrogenation of trifluoroacetate esters **S1-S3**.<sup>[a]</sup>



Entry	Sub.	Deviation from above	Yield TFE (%) <sup>[b]</sup>
1	<b>S1</b>	-	100 <sup>[d]</sup>
2	<b>S1</b>	without <b>1</b>	7 <sup>[d]</sup>
3	<b>S1</b>	without Me <sub>3</sub> NO	17 <sup>[d]</sup>
4	<b>S1</b>	+ Hg(0) [38 mol%]	100
5	<b>S1</b>	+ P(OMe) <sub>3</sub> [1.3 mol%]	100
6	<b>S1</b>	+ P(OMe) <sub>3</sub> [2.5 mol%]	36
7	<b>S1</b>	+ P(OMe) <sub>3</sub> [5.0 mol%]	16
8	<b>S2</b>	-	77
9	<b>S3</b>	-	82 <sup>[e]</sup>
10	<b>S2</b>	1,4-dioxane	100
11	<b>S2</b>	DCE	89
12	<b>S2</b>	toluene	100
13	<b>S3</b>	toluene	100

<sup>[a]</sup> Reaction conditions: substrate (1 mmol), **1** (2.5 mol%), Me<sub>3</sub>NO (5 mol%), P<sub>H2</sub> = 70 bar, solvent (0.75 mL), T = 110 °C, reaction time = 17 h. DCE = 1,2-dichloroethane; TFE = 2,2,2-trifluoroethanol. <sup>[b]</sup> Determined by <sup>19</sup>F{<sup>1</sup>H}-NMR analysis of the reaction crude.<sup>[10]</sup> <sup>[c]</sup> Mole balance (by <sup>19</sup>F{<sup>1</sup>H}-NMR, using α,α,α-trifluorotoluene as internal standard) = 89%, due to the low boiling point of **S1** and consequent loss during handling. <sup>[d]</sup> Formed by hydrolysis of **S1**, together with an equimolar amount of trifluoroacetic acid (TFA). <sup>[e]</sup> Mole balance = 99%.

As shown in Table 1 (entry 1), substrate **S1** was quantitatively hydrogenated to 2,2,2-trifluoroethanol (TFE) with no sign of hydrolysis to trifluoroacetic acid (TFA). In the absence of either complex **1** or Me<sub>3</sub>NO, no reduction took place (Table 1, entries 2 and 3), but TFE was detected due to hydrolysis of **S1**, as confirmed by the presence of equimolar amounts of TFA. Catalyst poisoning experiments were carried out *in operando*.<sup>[16]</sup> while the addition of an excess of Hg(0) did not affect the hydrogenation of **S1** (Table 1, entry 4), P(OMe)<sub>3</sub> led to a drop of conversion only when its amount was ≥ 1 equiv. to **1** (Table 1, entries 5-7). These data are consistent with a homogeneous

catalyst being operating. With the less activated substrates **S2** and **S3**, full conversion was not obtained (Table 1, entries 8, 9). However, when using pure 1,4-dioxane as a solvent and therefore adding Me<sub>3</sub>NO as a solid, **S2** was fully hydrogenated (Table 1, entry 10). Incomplete conversion was obtained in pure DCE (Table 1, entry 11), indicating that this solvent may have been the cause of the previously observed catalyst stalling. Toluene also allowed to obtain 100% yield for both **S2** and **S3** (Table 1, entries 12-13) and was selected as solvent for the rest of our study.

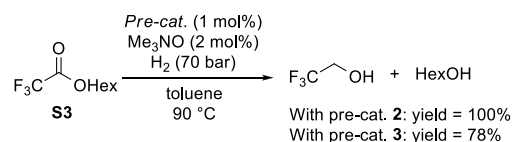
Further optimization of the reaction parameters was performed with substrate **S3** in toluene (Table 2). Decreasing the amount of pre-catalyst **1** from 2.5 to 1 mol% did not affect the yield, which remained quantitative both at 110 °C (Table 2, entry 2) and at 90 °C (Table 2, entry 3), corresponding to a TON of 100. Nearly quantitative yields were obtained also when temperature (Table 2, entry 4) or pressure (Table 2, entry 5) were further decreased to 70 °C and 35 bar, respectively. At 90 °C and under 70 bar of H<sub>2</sub>, the catalyst loading could be further reduced (Table 2, entries 6-8), leading to a decrease in conversion but an increase in TON.

**Table 2.** Optimization of reaction parameters in the hydrogenation of *n*-hexyl trifluoroacetate **S3** promoted by complex **1**.<sup>[a]</sup>

Entry	mol% <b>1</b>	T (°C)	P (bar)	Yield (%) <sup>[b]</sup>	TON
1	2.5	110	70	100	40
2	1	110	70	100	100
3	1	90	70	100	100
4	1	70	70	99	99
5	1	90	35	98	98
6	0.5	90	70	97	194
7	0.25	90	70	84	336
8	0.2	90	70	62	310

<sup>[a]</sup> Reaction conditions: substrate (1 mmol), **1** (x mol%), Me<sub>3</sub>NO (2x mol%), toluene (0.75 mL), reaction time = 17 h. <sup>[b]</sup> Determined by <sup>19</sup>F{<sup>1</sup>H}-NMR analysis of the reaction crude. No substrate hydrolysis observed in any case.

The known (cyclopentadienone)iron complexes **2** and **3** (Figure 2), screened in the hydrogenation of substrate **S3** under the optimized conditions, also showed catalytic activity (Scheme 1).



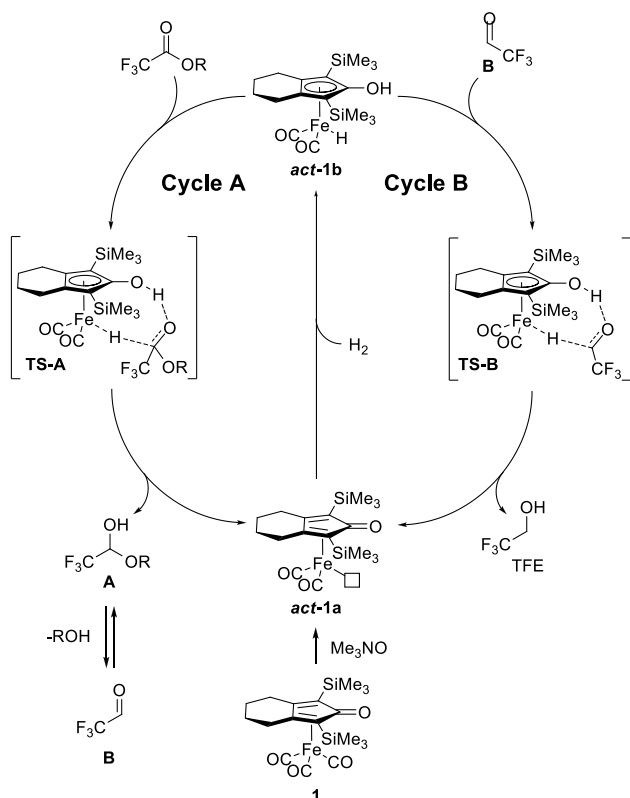
**Scheme 1.** Screening of (cyclopentadienone)iron complexes **2** and **3** in the hydrogenation of *n*-hexyl trifluoroacetate (**S3**).

The 3,4-ethylenediamino-substituted (cyclopentadienone)iron complex **3**, recently reported as very active in the hydrogenation of imines and NaHCO<sub>3</sub>,<sup>[7a]</sup> appeared to be slightly less active than pre-catalysts **1** and **2**.

Trifluoroacetates are prone to undergo hydrolysis with adventitious water, releasing TFA. Thus, before determining the substrate scope of pre-catalyst **1**, we decided to investigate



fact that conversion is observed only with trifluoroacetate esters, possessing the strongly electron-withdrawing group CF<sub>3</sub>.



**Scheme 2.** Tentative mechanism for the hydrogenation of trifluoroacetate esters promoted by pre-catalyst **1** upon activation with Me<sub>3</sub>NO.

In conclusion, we have demonstrated that air-stable and easy-to-make (cyclopentadienone)iron complexes such as **1** can be used as pre-catalysts for the hydrogenation of trifluoroacetate esters. The reaction, which occurs quantitatively at low catalyst loading (TON up to 336), has a broad substrate scope in terms of alkoxy residues, and bulky substituents are also tolerated. This study represents a remarkable expansion of the application scope of (cyclopentadienone)metal complexes in general (metal = Fe or Ru, in most cases), which did not include so far any ester substrate.<sup>[14,19]</sup> Moreover, to the best of our knowledge, this is the first example of Fe-catalyzed ester hydrogenation involving a cheap and stable pre-catalyst instead of costly and air-sensitive pincer complexes.<sup>[9,11b]</sup>

## Experimental Section

**General procedure for the ester hydrogenation screening.** In a nitrogen-filled mBraun glovebox, a solution of pre-catalyst (0.01 mmol, 1 mol% in 0.25 mL solvent) was dispensed to a glass vial containing solid Me<sub>3</sub>NO (0.02 mmol, 2 mol%). The vials were capped and the obtained solutions were stirred for 1 h at 30 °C. After this time, each vial was opened and a mixture of substrate (1 mmol) and TEA (0.2 mmol, 20 mol%) was added. The vials were capped again and put inside the Premex 96er Multireactor. The system was purged three times with nitrogen (10 bar) and three times with hydrogen (10 bar). The reaction vessels were pressurized at 70 bar, heated at 90 °C and stirred overnight. The reactions were cooled down and then, after releasing hydrogen, they

were flushed with nitrogen (10 bar). After adding α,α,α-trifluorotoluene (about 0.5 mmol), the crudes were analyzed by <sup>19</sup>F{<sup>1</sup>H} NMR.

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**Keywords:** iron • hydrogenation • homogeneous catalysis • ester reduction • (cyclopentadienone)iron complexes

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