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Fast and selective iron-catalyzed transfer hydrogenations of aldehydes

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Dedicated to Professor Dr. Dr. h.c. Wolfgang A. Herrmann on the occasion of his 65th birthday.

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ABSTRACT

An efficient iron-based catalyst system consisting of $Fe(BF)_4 \cdot 6H_2O$ and $P(CH_2CH_2PPh_2)_3$ [tetraphos, (PP_3)] is presented for the highly selective transfer hydrogenation of aromatic, aliphatic, and α,β-unsaturated aldehydes. A wide range of substrates including aldehydes with other reducible functional groups gave the corresponding alcohols in good yields. Formic acid is applied as a cheap, environmentally benign and easy to handle hydrogen source. Notable features of the presented methodology are the fast reactions under mild conditions. Advantageously compared to most transfer hydrogenations, no stoichiometric amounts of base additives are required.

1. Introduction

Catalytic transfer hydrogenations have received much attention in recent years as a benign and practical method for the reduction of carbonyl compounds [1]. Various catalyst systems were established especially for the reduction of ketones including chiral complexes [2]. In contrast, only few protocols have been developed for the transfer hydrogenation of aldehydes as it is more difficult to control the chemoselectivity of this transformation [3]. A general problem in these reactions is the use of base which is typically required in transfer hydrogenations. In the presence of base, deprotonation in the α-position of the carbonyl group takes place followed by aldol condensation. Another side-reaction is the possible CH_α-bond activation of the aldehyde [4]. The latter reaction is known to precede with rhodium [5] and iridium [6] complexes followed by decarbonylation. Beside the formation of alkanes, the carbonyl group may also block the catalyst. In addition, ruthenium- [7] or osmium-based systems [8] can lead to Tishchenko-type dimerization. Another problem in the hydrogenation of α,β-unsaturated aldehydes is the control of the chemoselectivity. From a thermodynamic point of view, the CC-double bond is more easily reduced compared to the aldehyde [9]. To overcome all these shortcomings highly selective catalytic systems need to be developed. Although protocols have been reported, based on iridium [3b,10], rhodium [11], ruthenium [3a,12], and nickel [13] catalysts, many of them lack selectivity and further improvements are highly desirable.

In the search for more efficient and environmentally benign catalytic systems, in the last decade the scientific focus shifted from the use of precious metals to their first row analogs. Especially iron catalysts received much attention as the metal is cheap, ubiquitous and relatively non-toxic [14]. Based on our experience in iron-catalyzed reductions [15], we became interested to develop a general iron-catalyzed transfer hydrogenation of aldehydes. Recently, we demonstrated that defined iron-tetraphos complexes allow for the selective reduction of nitroarenes to their corresponding anilines [16]. The best catalyst activity was observed in the absence of base, which makes it a rare example of a base-free transfer hydrogenation. Obviously, this might be favorable for the reduction of aldehydes as it avoids aldol condensations. To the best of our knowledge, iron is not known to insert into the CH_α-bond of the carbonyl group and therefore does not catalyze the decarbonylation of aldehydes [17]. Next to the nitro reduction, the selective hydrogenation of terminal alkynes to the corresponding alkenes is also possible with this type of iron catalyst [18]. Interestingly, it does not catalyze the reduction of CC-double bonds. This observation made it a promising candidate for the selective reduction of α,β-unsaturated aldehydes.

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2. Experimental

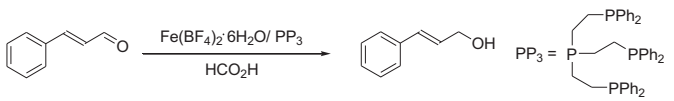
$Fe(BF_4)_2 \cdot 6H_2O$ (0.7 mg; 0.002 mmol) and tris[2-(diphenyl-phosphino)-ethyl]phosphine [$P(CH_2CH_2PPh_2)_3$; tetraphos] (1.4 mg; 0.002 mmol) are placed in a Schlenk-tube under argon atmosphere. 1 mL dry tetrahydrofurane is added and the purple solution is stirred for 2 min. Cinnamaldehyde (63 μL; 0.5 mmol) and 100 μL *n*-hexadecane as an internal GC-standard are injected and a sample is taken for GC-analysis. The solution is heated to 60 °C and the reaction starts by addition of 1.1 equiv formic acid (22 μL; 0.55 mmol). After 2 h, a second sample is taken for GC-analysis and conversion and yield are determined by comparison with authentic samples. For the isolation, the reaction is scaled up by a factor of 20. When the reaction is completed, the reaction solution is diluted with a mixture of *n*-hexane and ethyl acetate (3:1), filtered through a plug of silica and the solvent removed in vacuum.

3. Results and discussion

At the start of this project, we used cinnamaldehyde as the benchmark substrate for the reduction of unsaturated aldehydes. The catalytic experiments were performed in the presence of a combination of $Fe(BF)_4 \cdot 6H_2O$ and tris[2-(diphenyl-phosphino)-ethyl]phosphine [$P(CH_2CH_2PPh_2)_3$; (PP_3)] using formic acid (FA) as reducing agent (Table 1). The single components of the catalyst system did not show any reactivity at all while the combination of ligand and cationic iron species exhibited good conversion (Table 1, entries 2–4). Adding the ligand PP_3 to the iron salt the complex $[FeF(PP_3)][BF_4]$ is formed *in situ* which is indicated by a change of the colorless solution into deep purple. Next, the defined complex was applied under the same reaction conditions. As expected, reactivity comparable to the *in situ* system was obtained (Table 1, entry 5) [19]. Remarkably, in all the reactions the conjugated CC-double bond is not attacked. Decarbonylation, Tishchenko-type dimerization or aldol condensation is also not observed and full selectivity towards the cinnamyl alcohol is obtained.

Next, we investigated the influence of different solvents on the benchmark reaction. While in toluene no reactivity is observed, applying different alcohols and ether gave high to moderate conversions (Table 2). However, in alcohols the major products were the undesired hemiacetal and acetal. Here, cinnamic alcohol was obtained only in minor amount. Tetrahydrofurane led to the highest yields and therefore was chosen as the solvent for further reactions. As shown in Table 3, the reaction temperature has a major influence on the reactivity of the system. While the increase from 20 °C to 40 °C raised the conversion from 11% to 31%, a further increase to 60 °C led to full conversion (Table 3, entries 1–3).

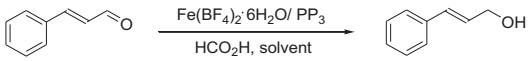
Table 1
Iron-catalyzed transfer hydrogenation of cinnamaldehyde: comparison of the *in situ*-generated system and the defined iron-tetraphos complex.[a]



Entry	Catalyst	Conv.[b] [%]	Yield[b] [%]	Selec.[b] [%]
1	–	–	–	–
2	$Fe(BF_4)_2 \cdot 6H_2O$	–	–	–
3	PP_3	–	–	–
4	$Fe(BF_4)_2 \cdot 6H_2O/PP_3$	31	31	>99
5	$[FeF(PP_3)][BF_4]$	30	30	>99

[a] Reactions conditions: 0.5 mmol cinnamaldehyde, 0.75 mol% catalyst, 1 mL THF, 2 equiv FA, 40 °C, 2 h.
[b] Determined by GC using *n*-hexadecane as an internal standard.

Table 2
Iron-catalyzed selective reduction of cinnamaldehyde: influence of solvents.[a]



Entry	Solvent	Conv.[b] [%]	Yield[b] [%]	Selec.[b] [%]
1	Toluene	–	–	–
2	MeOH	70	5	7
3	*i*-PrOH	25	16	64
4	THF	31	31	99
5	EtOH	48	16	33
6	2-Me-THF	9	9	99
7	*t*-AmOH	14	14	99

[a] Reactions conditions: 0.5 mmol cinnamaldehyde, 0.75 mol% $[FeF(PP_3)][BF_4]$, 1 mL solvent, 2 equiv FA, 40 °C, 2 h.
[b] Determined by GC using *n*-hexadecane as an internal standard.

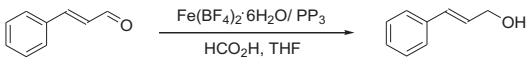
Variation of the catalyst concentration (Table 3, entries 4–7) demonstrated that 0.5 mol% of the catalyst is sufficient to maintain complete conversion and quantitative yield.

Best results were obtained applying one equivalent of formic acid (Table 3, entries 8–11). This finding is in contrast to our previous reductions of nitroarenes, where an excess of reducing agent was required due to partly decomposition of formic acid into hydrogen and carbon dioxide [16]. Apparently, under the present conditions such decomposition of formic acid does not take place and no increase of pressure is observed. Using lower amounts of acid led to no complete conversion (Table 3, entry 8).

The highest yield was obtained using a catalyst loading of 0.4 mol % and a slight excess of 1.1 equivalents of formic acid (Table 3, entry 12). Notably, the reaction time can be significantly reduced at higher catalyst loading. Hence, applying 2 mol% of catalyst complete conversion was obtained within only 10 min (Table 3, entry 13).

Next, we investigated the general applicability of our catalyst system. First, we focused on the reactivity of different α,β-unsaturated aldehydes (Table 4). Cinnamaldehydes bearing substituents in

Table 3
Optimization of selected reaction parameters for the selective reduction of cinnamaldehyde.[a]



Entry	Catalyst loading [mol%]	Conv.[b] [%]	Yield[b] [%]	Selec.[b] [%]
1[c]	0.75	11	11	>99
2[d]	0.75	31	31	>99
3	0.75	100	>99	>99
4	0.2	20	20	>99
5	0.3	31	31	>99
6	0.4	40	40	>99
7	0.5	100	>99	>99
8[e]	0.3	75	75	>99
9[f]	0.3	97	97	>99
10[g]	0.3	83	83	>99
11[h]	0.3	60	60	>99
12[i]	0.4	100	>99	>99
13[j]	2.0	100	>99	>99

[a] Reactions conditions: 0.5 mmol cinnamaldehyde, 1 mL THF, 2 equiv FA, 60 °C, 2 h.
[b] Determined by GC using *n*-hexadecane as an internal standard.
[c] 20 °C.
[d] 40 °C.
[e] 0.75 equiv FA.
[f] 1 equiv FA.
[g] 1.25 equiv FA.
[h] 1.5 equiv FA.
[i] 1.1 equiv FA.
[j] 10 min.

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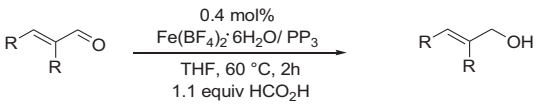
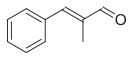
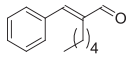
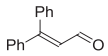
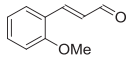
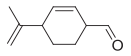
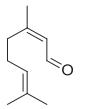
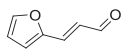
Table 4
Iron-tetraphos catalyzed reduction of α,β-unsaturated aldehydes.[a]



Entry	Substrate	Conv.[b] [%]	Yield[b] [%]	Selec.[b] [%]
1		>99	99	99
2[c]		>99	99 (99)	99 (99)
3		>99	99	99
4[d]		>99	99	99
5		>99	99	99
6		>99	99	99
7		>99	99	99
8[c]		>99	(96)	(96)

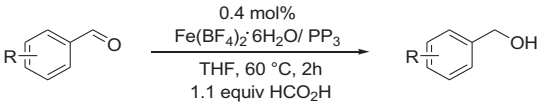
[a] Reactions conditions: 0.5 mmol substrates, 0.4 mol% $Fe(BF_4)_2 \cdot 6H_2O/PP_3$, 1 mL THF, 1.1 equiv FA, 60 °C, 2 h.
[b] Determined by GC using *n*-hexadecane as an internal standard.
[c] Scaled up by the factor 20, isolated yield given in brackets.
[d] 1 mol% catalyst loading.

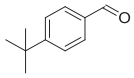
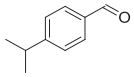
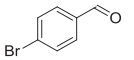
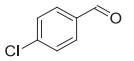
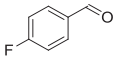
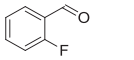
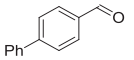
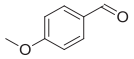
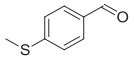
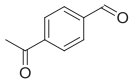
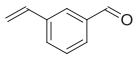
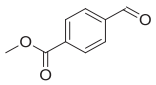
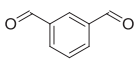
the α- or β-position showed excellent reactivity and gave up to 99% yield (Table 4, entries 1–3). Cinnamaldehyde with a methoxy-substituent in the ortho-position of the aromatic ring was fully converted to the corresponding cinnamyl alcohol but required a higher catalyst loading of 1 mol% (Table 4, entry 4). Furthermore, we tested different naturally occurring terpenes (Table 4, entries 5–7). To our delight, in each case quantitative yield was achieved and no side products were observed. Similarly, the heteroaromatic 2-furanacrolein gave the corresponding unsaturated alcohol in excellent yield (99%; Table 4, entry 8).

To explore the functional group tolerance in more detail, we started to investigate reactions of different substituted benzaldehydes (Table 5). First, simple benzaldehyde was fully converted to benzyl alcohol (Table 5, entry 1). Benzaldehydes bearing different alkyl groups gave yields of 97% and 99%, respectively (Table 5, entries 2 and 3). Halogen-substituted substrates also showed full conversion (Table 5, entries 4–7), and the position of the halide substituent had no influence on the reactivity (Table 5, entries 6 and 7). Ether- and thioether-substituted benzaldehydes yielded the corresponding alcohols again in nearly quantitative yield (99%; Table 5, entries 9 and 10). Remarkably, benzaldehydes with sensitive functional groups such as vinyl, acetyl and ester were reduced with excellent chemoselectivity and the different reducible substituents were not attacked under these conditions (Table 5, entries 11–13). In the case of the isophthalaldehyde both formyl groups were reduced giving a TON of 500 (Table 5, entry 14).

Next, transfer hydrogenations of different heterocyclic and aliphatic aldehydes were performed (Table 6). While for furan-2-

Table 5
Iron-tetraphos catalyzed reduction of benzaldehydes bearing different functional groups.[a]



Entry	Substrate	Conv.[b] [%]	Yield[b,c] [%]	Selec.[b,c] [%]
1		>99	96	96
2		>99	97	97
3		>99	99	99
4		>99	98	98
5		>99	97	97
6		>99	99	99
7		>99	98	98
8		>99	99	99
9		>99	99	99
10		>99	99	99
11[d]		>99	99 (98)	99 (98)
12[e]		>99	99 (99)	99 (99)
13[f]		>99	99 (97)	99 (97)
14[g]		>99	99	99

[a] Reactions conditions: 0.5 mmol substrates, 0.4 mol% $Fe(BF_4)_2 \cdot 6H_2O/PP_3$, 1 mL THF, 1.1 equiv FA, 60 °C, 2 h.
[b] Determined by GC using *n*-hexadecane as an internal standard.
[c] Isolated yield given in brackets.
[d] Scaled up by the factor 6.
[e] Scaled up by the factor 20.
[f] Scaled up by the factor 5.
[g] 2.2 equiv FA, product is the 1,3-benzenedimethanol.

aldehyde and 2-thiophenecarboxaldehyde full conversion was achieved, the 2-pyridinecarboxaldehyde yielded only traces of the corresponding alcohol (Table 6, entries 1–3). A similar behavior was observed in the reduction of 3-ethynylpyridine, which yielded only traces of the corresponding vinyl compound [18]. Finally, we tested the aliphatic aldehydes octanal and the sterically demanding 2,2-diphenylcarboxaldehyde (Table 6, entries 4 and 5). In both cases

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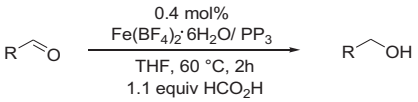
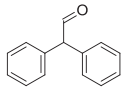
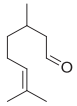
Table 6
Different heteroaromatic and aliphatic aldehydes in the iron-tetraphos catalyzed transfer hydrogenation.[a]



Entry	Substrate	Conv.[b] [%]	Yield[b] [%]	Selec.[b] [%]
1		>99	99	99
2		<1	<1	–
3		>99	99	99
4		>99	98	98
5		>99	96	96
6		>99	97	97

[a] Reactions conditions: 0.5 mmol substrates, 0.4 mol% $Fe(BF_4)_2 \cdot 6H_2O/PP_3$, 1 mL THF, 1.1 equiv FA, 60 °C, 2 h.
[b] Determined by GC using *n*-hexadecane as an internal standard.

excellent yields of the corresponding alcohols were obtained. Also the industrial important aliphatic aldehyde citronellal was subjected to the reaction conditions and was fully converted to yield citronellol in 97%.

In conclusion, we have developed an efficient iron-tetraphos catalyzed system for the highly selective transfer hydrogenation of aromatic, aliphatic and α,β-unsaturated aldehydes towards their alcohols. In none of the reactions any significant amounts of side-products were observed. A wide range of functional groups, especially other reducible moieties, are tolerated. The reaction proceeds fast and under mild conditions. Formic acid is applied as a cheap, environmentally benign and easy to handle hydrogen source. Notably, no base is required leaving it a rare example of a base-free transfer hydrogenation.

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