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Hydrogenation of nitroarenes using defined iron–phosphine catalysts†

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A novel iron-catalyzed hydrogenation of nitroarenes to the corresponding amines is reported. An *in situ* combination of $Fe(BF_4)_2 \cdot 6H_2O$ and phosphine allows for highly selective hydrogenation of a broad range of aromatic and nitroarenes tolerating different functional groups.

Aniline and its derivatives are important building blocks for the production of dyes, pigments, agrochemicals, and pharmaceuticals produced annually on bulk industrial scale.[1] In general, they are prepared *via* direct hydrogenation using heterogeneous catalysts. Applying more complex substrates these catalysts can cause side-reactions such as dehalogenation processes in the case of halonitroarenes or unselective reduction of other reducible moieties. To overcome these limitations, in organic synthesis on the laboratory scale stoichiometric methods based on reducing agents such as Fe, Zn, Sn or Al and the sulphide reduction are still popular.[2] From ecological and economic points of view hydrogen is the preferred reducing agent, because only water is formed as a by-product. Thus, numerous attempts have been made to modify common heterogeneous catalysts to achieve high chemoselectivities.[3] Notably, significant progress was achieved by Corma and co-workers who developed a specific gold catalyst for a general reduction of nitroarenes.[4] Most recently, we also developed a novel cobaltoxide-based catalyst which allows for broad functional group tolerance.[5]

Another approach to control selectivity for nitroarene reduction is working with organometallic complexes. The well-defined structure of the catalyst can be tuned easily to direct the selectivity towards the desired product. Choosing the right combination of the metal and the ligand can lead to significant improvements. Although it is clear that homogeneous catalyst systems will not be used in existing continuously driven processes, they are interesting for the production of specialties and synthetic applications. For this purpose various hydrogenation protocols primarily based on Au,[6] Pt,[7,8] Rh,[9,11] Pd,[6,8,10] Ir[11] and Ru[8,12] have been developed in the last decades.

On the way to a more sustainable chemistry, the replacement of precious metals by non-noble metals is a major goal. In this respect, iron as an abundant, non-toxic and cheap metal is an ideal candidate for the development of environmentally benign processes. Significant achievements have been realized in recent years in this area.[13] In contrast to precious metals, molecular-defined hydrogenation catalysts based on iron have been scarcely studied. In fact, for the iron-catalyzed hydrogenation of nitroarenes only two protocols have been developed. Knifton applied an $Fe(CO)_3(PPh_3)_2$ catalyst at 80 bar hydrogen pressure for 9 hours at 125 °C to obtain moderate yields.[12a] On the other hand Chaudhari *et al.* used a system consisting of $Fe(SO_4) \cdot 7H_2O$ and Na_2EDTA operating *in situ* at high temperature (150 °C) in a biphasic medium.[14]

Based on our experience in the field of iron-catalyzed reductions,[15] we became interested in applying iron–phosphine complexes for this transformation.[16] In this respect, recently we developed an iron–phosphine based catalyst for the mild and selective transfer hydrogenation of nitroarenes.[17] Here, formic acid is used as a stoichiometric reducing agent. Although the system is attractive for laboratory scale production, it produces carbon dioxide as a side product and is also corrosive because of the high concentration of formic acid. In contrast, in industry the direct hydrogenation with molecular hydrogen is favoured as green technology. Hence, we wanted to adopt this catalyst system for the direct hydrogenation of nitroarenes.

Initially, we tested the *in situ* generated catalyst of $Fe(BF_4)_2 \cdot 6H_2O$ with the ligand tris[(2-diphenylphosphino)ethyl]-phosphine [$P(CH_2CH_2PPh_2)_3$; **L1**] and the defined complex [FeF(**L1**)][BF_4] for the direct hydrogenation of nitrobenzene (Table 1, entries 7 and 8). A reaction temperature of 120 °C and 30 bar pressure were chosen initially for hydrogen activation. After two hours, a minor conversion of 9% was observed, indicating some reactivity of the catalyst. We assumed that due to the high reaction temperature the ligand is partly decomposed. Unfortunately, at lower temperature no reactivity is observed. Hence, we started to synthesize the thermally more stable tris[(2-diphenylphosphino)phenyl]-phosphine ligand [$P(PhPPh_2)_3$; **L2**] where the phosphorus atoms are bridged by phenylene moieties.

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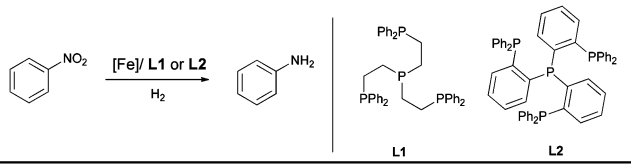
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c3cc42983k

Table 1 Iron-catalyzed hydrogenation of nitrobenzene[a]



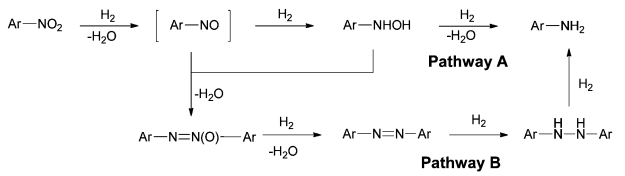
Entry	Catalyst	Conv.[b] (%)	Yield[b] (%)	Select. (%)
1	—	<1	<1	<1
2	$Fe(BF_4)_2{\cdot}6H_2O$	<1	<1	<1
3	**L2**	<1	<1	<1
4	20 μL TFA	<1	<1	<1
5[c]	$Fe(BF_4)_2{\cdot}6H_2O$	<1	<1	<1
6[c]	**L2**	<1	<1	<1
7[c]	$Fe(BF_4)_2{\cdot}6H_2O$/**L1**	9	5	56
8[c]	[FeF(**L1**)][BF_4]	9	9	>99
9[c]	$Fe(BF_4)_2{\cdot}6H_2O$/**L2**	49	49	>99
10[c]	[FeF(**L2**)][BF_4]	48	48	>99

[a] Reaction conditions: 0.5 mmol nitrobenzene, 1 mol% catalyst, 120 °C, 2 h, 30 bar H_2, 1.5 mL THF. [b] Determined by GC using *n*-hexadecane as an internal standard. [c] Addition of 50 mol% (20 μL) TFA.

To our delight, applying either the *in situ* system or the defined complex [FeF(**L2**)][BF_4] significantly higher conversions of 49% and 48%, respectively, were obtained under the same reaction conditions (Table 1, entries 9 and 10). The similar reactivity of the *in situ* catalyst and the defined complex showed that both systems formed the same active species in solution. Further, we tested the different components of the system to exclude simple iron-, acid- or ligand-catalyzed reaction (Table 1, entries 1–6). In none of these reactions any reactivity was observed proving the [FeF(**L2**)][BF_4] to be the real pre-catalyst.

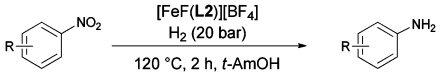
Next, the reaction parameters were optimized to increase the reactivity of this system (ESI†). The selectivity of the catalyst in tertiary alcohols such as *tert*-amylalcohol is superior, while the deployment of tetrahydrofuran led to similar results. Notably, addition of acid is required to obtain significant hydrogenation activity, which is different from most noble metal-based hydrogenation catalysts. By testing the influence of different acids, significant reactivity is obtained only in the presence of strong acids such as trifluoroacetic acid (TFA). Further, the effect of the concentration of TFA was examined. The addition of one equivalent (with respect to the substrate) is most favourable. Investigating the dependency of the conversion on the hydrogen pressure showed best results between 10–20 bar of hydrogen at 120 °C. Finally, a catalyst concentration of 2 mol% was chosen to ensure complete conversion of the substrate to give a quantitative yield of aniline.

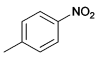
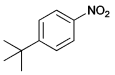
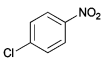
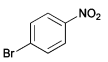
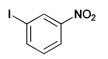
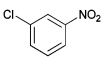
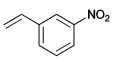
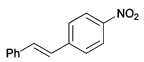
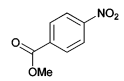
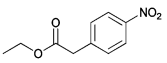
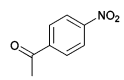
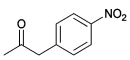
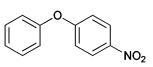
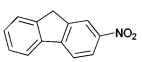
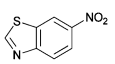
An important aspect in the industrial reduction of nitroarenes is the accumulation of toxic and/or explosive intermediates (Scheme 1).[18] Under our conditions we did not detect any formation of such intermediates. Two pathways are considered for the reduction of nitrobenzene; the direct reduction to aniline (A) and the dimerization *via* azobenzene (B). To elucidate the preferred pathway with our system, we performed catalytic hydrogenations with *N*-phenylhydroxylamine as well as diazobenzene. In both cases, full conversion was achieved at a similar rate. Thus, both reaction pathways seem to be possible in the present system.



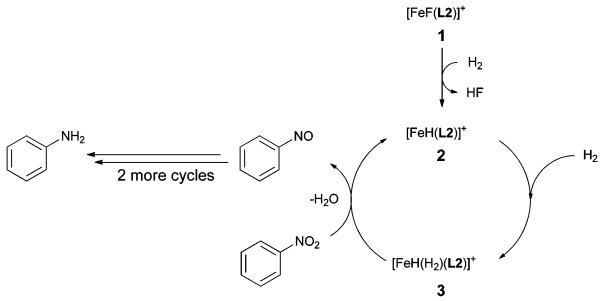
Scheme 1 Possible reaction pathways for the catalytic hydrogenation of nitrobenzene.

Table 2 Iron-tetraphos-catalyzed reduction of nitroarenes[a]



Entry	Substrate, R =	Cat. (mol%)	Conv.[b] (%)	Yield[b,c] (%)
1		2	>99	99
2		2	>99	96 (93)
3		2	>99	99 (92)
4		5	>99	98
5		4	>99	99 (90)
6		4	>99	99
7		4	>99	97
8		4	>99	98
9		3	>99	99
10		2	>99	98
11		4	>99	99 (92)
12		5	>99	97 (91)
13[d]		5	>99	99
14		2	>99	99 (94)
15		5	>99	99
16		4	>99	91
17[d]		4	>99	91
18		4	>99	78

[a] Reaction conditions: 120 °C, 0.5 mmol substrate, 20 bar H_2, 1.5 mL *t*-AmOH, 40 μL TFA, 2 h. [b] Determined by GC using *n*-hexadecane as an internal standard. [c] Isolated yields given in brackets. [d] 80 μL TFA.



Scheme 2 Proposed simplified catalytic cycle for the iron-catalyzed hydrogenation of nitrobenzene.

Next, we investigated the substrate scope of our iron-based catalyst system (Table 2). Nitrotoluenes and related derivatives including bulky *ortho*-substituted nitroarenes were hydrogenated giving quantitative yields (Table 2, entries 2–4). Halide-containing substrates were also fully converted albeit a higher catalyst loading is required (Table 2, entries 5–8). More demanding nitroarenes bearing other reducible moieties were studied, too (Table 2, entries 9–15). Notably, substrates with C–C-double bonds, esters, and ketone functionalities can be smoothly hydrogenated with excellent selectivity leaving the additional substituent unaffected. Further, we tested different heteroaromatic nitro compounds due to the importance of the corresponding anilines as valuable intermediates for pharmaceuticals and agrochemicals.[19] Gratifyingly, 6-nitrobenzothiazol and 8-nitroquinoline were fully reduced to the corresponding amines. In order to achieve complete conversion, an additional amount of TFA was necessary to block the heterocyclic nitrogen atom from coordinating to the catalyst (Table 2, entries 17 and 18). To get more insight into the catalytic cycle, ^{1}H and ^{31}P NMR experiments were performed under the standard reaction conditions. First, the reaction solution without the substrate was investigated at room temperature under argon atmosphere. No NMR signal is detectable as the [FeF(**L2**)][BF_4]-complex is paramagnetic. Pressurising the reaction solution with 20 bar of hydrogen resulted in partial formation of the diamagnetic iron hydride complex [FeH(H_2)(**L2**)][BF_4] which is characterized by its ^{1}H NMR signal at −9.18 ppm and two ^{31}P NMR signals at 142.9 ppm (quartet) and 87.6 ppm (doublet) (ESI†). Raising the temperature to 80 °C increased the formation of this hydrogenated complex. At a temperature of 120 °C the signals of the complex could be detected only in the ^{31}P NMR spectra due to the reduced intensity of the signals. The addition of nitrobenzene at 60 °C resulted in an immediate disappearance of the ^{1}H and ^{31}P NMR signals of the complex [FeH(H_2)(**L2**)][BF_4]. After two hours at 120 °C nitrobenzene was fully converted to aniline. As a result at 60 °C the complex [FeH(H_2)(**L2**)][BF_4] was detected again by NMR.

Thus, we propose a simplified catalytic cycle (Scheme 2). The defined pre-catalyst [FeF(**L2**)]$^+$ (**1**) is hydrogenated in two steps. Firstly, fluoride is replaced by a hydride while hydrogen fluoride is released and the complex [FeH(**L2**)]$^+$ (**2**) is formed as part of the catalytic cycle. Subsequently, **2** is hydrogenated to give [FeH(H_2)(**L2**)]$^+$ (**3**).[20] Complex **3** reduces nitroarenes to the corresponding nitrosoarenes. In parallel, complex **2** is formed, which is hydrogenated again to regenerate **3**. Two further consecutive hydrogenations led to the formation of anilines. In contrast to our previous report on the mechanism of the transfer hydrogenation,[17] the fluoride substituent does not play a significant role in the catalytic cycle. To support this assumption, we varied the iron source and tested the different *in situ* generated catalyst systems. Although $Fe(BF_4)\cdot 6H_2O$, which forms species **1** with the ligand **L2**, serves as the best metal precursor, also the fluoride-free $Fe(acac)_2$ and $Fe(OAc)_2$ led to active catalyst systems (ESI†). It should be noted that these iron precursors cannot be used in related transfer hydrogenations.

In summary, we have developed a molecularly-defined iron-based catalyst for the hydrogenation of nitroarenes. In the presence of the phosphine ligand **L2** the resulting stable iron complex is able to activate hydrogen. After optimization, a variety of functionalized nitroarenes as well as heteroaromatic nitro compounds were successfully hydrogenated to their corresponding amines while other reducible moieties such as vinyl or acetyl groups remained unaffected.

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