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An Easy and General Iron-catalyzed Reductive Amination of Aldehydes and Ketones with Anilines

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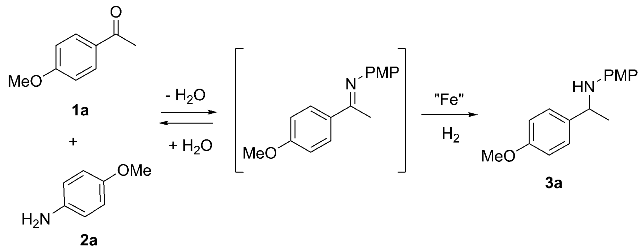
Alkylated anilines are used for a variety of applications in the food, pharmaceutical, agrochemical, dye, and polymer industries.[1] In general, the condensation of industrially available anilines with aldehydes and ketones and subsequent hydrogenation constitutes a straightforward approach for their synthesis. Although during the last two decades procedures for the highly selective catalytic reduction of imines have been developed,[2] unfortunately in these procedures the imine has to be synthesized and isolated in an additional step. Thus, the reductive amination of aldehydes and ketones constitutes a more efficient and direct route for their synthesis.[3] In the past, this route has employed reducing agents, including *iso*-propanol,[4] formates,[5] and so-called Hanztsch esters,[6] as well as silanes.[7] Clearly, the most atom economic and environmentally friendly approach is the use of molecular hydrogen[8] for the reduction step with water as the only side-product in the overall transformation. The majority of the known catalysts for the latter reductive aminations are based on precious metal complexes of rhodium, iridium, and ruthenium.[9] Owing to the comparably high price of these precious metals and their corresponding complexes, the search for more economical and environmentally friendly catalysts is an ongoing and challenging research topic. In this respect, novel catalysts based on iron, copper, zinc, or manganese offer particularly attractive options.[10] Although iron is the second most abundant metal in the earth's crust, it has only been scarcely investigated for reductive aminations.[11] More recently, Enthaler showed that a reductive amination of aldehydes is possible with simple $FeCl_3$ using silanes.[12] Notably, iron-carbonyl complexes $Fe_x(CO)_y$ were found to be active in the hydrosilylation of alkenes and the reduction of amides.[13] Based on these results and our experience in iron-catalyzed reductions of C=X bonds,[13c,14] we started to investigate the reductive amination of carbonyl compounds in the presence of iron catalysts. As a result, herein, we report inexpensive $Fe_3(CO)_{12}$ as a convenient homogeneous catalyst system which allows for the reductive amination of aldehydes and ketones under mild conditions using molecular hydrogen. In exploratory studies, different iron sources were tested in the model reaction of 4-methoxyacetophenone **1a** and 4-anisidine **2a** at 50 bar hydrogen pressure and 65 °C. Molecular sieves were added to the reaction mixture to shift the equilibrium towards the in situ generated imine by removing water, which is formed during the condensation step. As shown in Table 1, iron(II)- and iron(III)-salts as well as [Fe(cot)(CO)$_3$] did not show any activity in the model reaction (Table 1, entries 2–6); in the presence of these iron salts and complexes, only the corresponding imine was formed. Surprisingly, other iron-carbonyl complexes showed significant activity in the model reaction (Table 1, entries 7–9). As $Fe_3(CO)_{12}$ turned out to be the most-active precursor, different catalyst loadings were tested with this complex (Table 1, entries 9–12). To our delight, the yield raised from 29 % to 84 % by increasing the catalyst loading from 1 to 4 mol %. Next, the influence of the reaction temperature was investigated in the model system (Table 1, entries 11, 13, 14). At 35 °C and 100 °C, only low yields (9 and 40 %, respectively) were observed. In both cases, the reduction of the preformed imine was not complete, which can be explained by either low activity (35 °C) or partial decomposition (100 °C) of the reduction catalyst.

Table 1. Reductive amination of 4-methoxyacetophenone with 4-anisidine.[a]



No	Iron precursor (mol %)	Solvent	Conv. [%]	Yield [%]
1[b]	—	toluene	92	–
2	$Fe(ClO_4)_2 \cdot xH_2O$ (10)	toluene	90	–
3	$Fe(OAc)_2$ (10)	toluene	45	–
4	$FePO_4 \cdot 6H_2O$ (10)	toluene	96	–
5	$Fe(NO_3)_3 \cdot 9H_2O$ (10)	toluene	>99	–
6	[Fe(cot)(CO)$_3$] (10)	toluene	99	–
7	[Et$_3$NH][HFe$_3$(CO)$_{11}$] (10)	toluene	61	1
8	$Fe_2(CO)_9$ (5)	toluene	>99	7
9[b]	$Fe_3(CO)_{12}$ (1)	toluene	71	29
10[b]	$Fe_3(CO)_{12}$ (2)	toluene	76	51
11[b]	$Fe_3(CO)_{12}$ (4)	toluene	92	84
12[b]	$Fe_3(CO)_{12}$ (6)	toluene	92	86
13[c]	$Fe_3(CO)_{12}$ (4)	toluene	83	9
14[d]	$Fe_3(CO)_{12}$ (4)	toluene	83	40
15[e]	$Fe_3(CO)_{12}$ (4)	toluene	33	31
16	$Fe_3(CO)_{12}$ (4)	toluene	>99	93
17	$Fe_3(CO)_{12}$ (4)	THF	29	3
18	$Fe_3(CO)_{12}$ (4)	1,4-dioxane	33	31
19	$Fe_3(CO)_{12}$ (4)	NMP	45	32
20	$Fe_3(CO)_{12}$ (4)	DMF	3	4

[a] General reaction conditions: 0.5 mmol 4-methoxyacetophenone **1a**, 0.75 mmol 4-anisidine, 200 mg 3 Å molecular sieve, 50 bar H_2, 65 °C, 24 h; [b] 0.5 mmol 4-anisidine **2a**; [c] 35 °C; [d] 100 °C; [e] without molecular sieves. cot = cyclooctatetraene. 1,4-dioxane.

Variation of the solvent showed that toluene is superior to the more polar tetrahydrofuran, 1,4-dioxane, 1-methyl-2-pyrrolidone (NMP), and *N*,*N*-dimethylformamide (DMF; Table 1, entries 17–20). Applying a 1.5 fold excess of 4-anisidine **2a** had a beneficial effect on the product yield. Under optimized conditions, 0.5 mmol 4-methoxyacetophenone, 0.75 mmol 4-anisidine, and 0.02 mmol $Fe_3(CO)_{12}$ smoothly underwent direct reductive amination with hydrogen to give 93 % of the corresponding amine **3a**.

In order to confirm that the observed catalyst activity was not caused by other metal impurities, we investigated possi-

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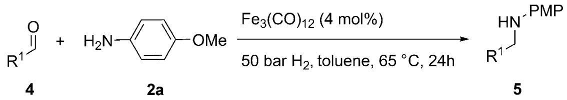
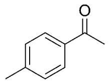
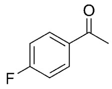
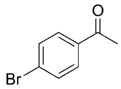
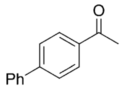
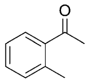
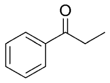
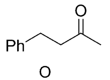
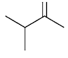
ble contaminations and analyzed $Fe_3(CO)_{12}$ by atomic absorption spectroscopy (AAS) and inductively coupled plasma mass spectrometry (ICP-MS). However, all other metals were found to be present below the detection limits of these methods (see the Supporting Information).[15] Furthermore, the reaction was performed using new glass vials and stirring bars and the control experiment without iron precursor did not show any product formation (Table 1, entry 1), which confirms the catalytic nature of the iron species.

With the optimized reaction conditions in hand, we explored the scope and limitations of this convenient iron-catalyzed reductive amination procedure. As shown in Table 2, a variety of substituted acetophenones were smoothly aminated and hydrogenated in high yields. Both electron-donating and electron-withdrawing substituents on the aromatic rings had little impact on the reductive amination activity, and high yields were also observed for substituted 2-arylmethylketones (83–97 % yield; Table 2, entries 1–4). The steric hindrance of the aryl group had no significant effect on the activity, as both *ortho-* and *para*-methyl-substituted acetophenones gave similar yields (Table 2, entries 1 and 5). Linear and α-branched aliphatic ketones reacted well, leading to high yields of the corresponding amine (95 and 93 %, respectively; Table 2, entries 7 and 8).

Table 2. Reductive amination of different ketones with 4-anisidine.[a]



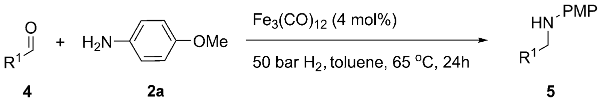
Entry	Ketones		Yield [%]
1[b]		**1a**	83
2		**1b**	91
3		**1c**	92
4		**1d**	97
5		**1e**	82
6		**1f**	91
7[b]		**1g**	95
8		**1h**	93

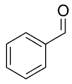
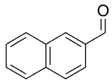
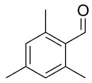
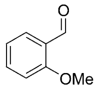
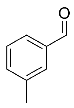
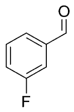
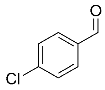
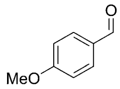
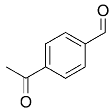
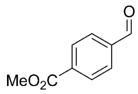
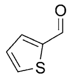
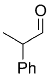
[a] General reaction conditions: 0.5 mmol ketone **1**, 0.75 mmol 4-anisidine **2a**, 200 mg 3 Å molecular sieve 16 h; 0.02 mmol $Fe_3(CO)_{12}$, 50 bar H_2, 65 °C, 24 h; [b] reaction conditions: 0.5 mmol ketone **1**, 0.75 mmol 4-anisidine **2a**, 0.02 mmol $Fe_3(CO)_{12}$, 50 bar H_2, 65 °C, 24 h.

Next, we examined the reductive amination of a range of aldehydes (**4**). Gratifyingly, the hydrogenative reductive amination of a number of aldehydes, including aromatic, heteroaromatic, and α-branched aldehydes proceeded in good to excellent yields (Table 3, entries 1–12).

As the equilibrium of the condensation reaction of benzaldehyde **4a** with 4-anisidine **2a** is almost completely shifted to the imine, the addition of molecular sieves is not nec-

Table 3. Reductive amination of different aldehydes with 4-anisidine.[a]

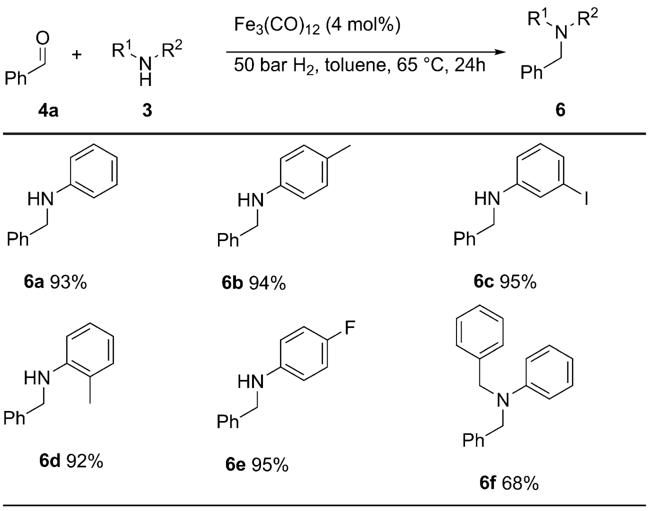


Entry	Aldehydes		Yield [%]
1		**4a**	97
2		**4b**	91
3		**4c**	95
4		**4d**	88
5		**4e**	95
6		**4f**	91
7		**4g**	73
8		**4h**	87
9		**4i**	89
10		**4j**	91
11		**4k**	90
12		**4l**	88

[a] General reaction conditions: 0.5 mmol aldehyde **4**, 0.75 mmol 4-anisidine **2a**, 0.02 mmol $Fe_3(CO)_{12}$, 50 bar H_2, 65 °C, 24 h.

essary for the reductive amination of aldehydes. *Ortho*-, *meta*- and *para*-substituted benzaldehydes with electron-donating and electron-withdrawing groups were reacted in high yields (Table 3, entries 1–12). Noteworthy, keto- and ester-goups were tolerated and the aldehyde reacted selectively to form the corresponding amines (Table 3, entries 9 and 10, respectively). The catalytic activity did not decrease by applying sterically demanding aldehydes, such as 2,4,6-trimethylbenzaldehyde **4c** (Table 3, entry 3). Furthermore, an excellent product yield of 90 % was obtained with thiophene-2-carbaldehyde **4k**, whilst the reductive amination of pyridine-3-carbaldehyde did not furnish the desired product, probably owing to the coordination of pyridine to the iron catalyst. Finally, the reductive amination of different amines with benzaldehyde **4a** was investigated. *Ortho*-, *meta*- and *para*-substituted anilines with electron-donating and electron-withdrawing groups reacted with benzaldehyde under hydrogenative conditions in high yields of 95 % (Table 4).

Table 4. Reductive amination of benzaldehyde with different anilines.



Unfortunately, under optimized conditions the reaction of aliphatic amines, such as *n*-butylamine or 2-ethylhexylamine, with benzaldehyde **4a** gave only the corresponding imine and no hydrogenation was observed. On the other hand, secondary amines, such as *N*-benzylaniline can be used to gain access to tertiary amines.

In summary, we have reported the first homogeneous iron-based catalyst system for the reductive amination of aldehydes and ketones using molecular hydrogen. Whilst numerous precious-metal-based catalysts are known, iron has been scarcely investigated in such catalytic reductions.

More specifically, we demonstrated that inexpensive triiron dodecacarbonyl can catalyze the direct hydrogenative reductive amination of carbonyl compounds with various anilines without the need of any special or expensive ligand. Good to excellent yields of 68–97 % have been achieved for a range of aryl, alkyl, and heterocyclic ketones as well as aldehydes with primary and secondary anilines.

Experimental Section

All experiments were done in 4 mL glass vials. Brand-new glass vials were placed in a Parr Instruments 4560 series autoclave (300 mL) containing an alloy plate that holds seven 4 mL glass vials.

General Procedure for the Hydrogenative Reductive Amination of Ketones

A: A vial was charged under an argon atmosphere with ketone **1** (0.5 mmol), 4-anisidine **2a** (0.75 mmol), $Fe_3(CO)_{12}$ (0.02 mmol), 3 Å molecular sieves (200 mg), dry toluene (1.0 mL), and a magnetic stirring bar and capped with a septum which was equipped with a needle. The vial was placed in the alloy plate, which was then placed into the pre-dried autoclave. Once sealed, the autoclave was purged 3 times with hydrogen, then pressurized to 50 bar, heated at 65 °C, and stirred for 24 h. The autoclave was cooled to 5 °C, depressurized, the reaction mixture was transferred into a flask, evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: heptane/ethyl acetate 20:1 to 10:1) to give the corresponding amine **3**.

B: A vial was charged under an argon atmosphere with ketone **1** (0.5 mmol), 4-anisidine **2b** (0.75 mmol), 3 Å molecular sieves (200 mg), dry toluene (1.0 mL), and a magnetic stirring bar and capped with a septum. The mixture was stirred for 16 h at room temperature. $Fe_3(CO)_{12}$ (0.02 mmol) was added, the vial was placed in the alloy plate, which was then placed into the pre-dried autoclave. Once sealed, the autoclave was purged 3 times with hydrogen, then pressurized to 50 bar, and heated at 65 °C for 24 h. The autoclave was cooled to 5 °C, depressurized, the reaction mixture was transferred into a flask, evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: heptane/ethyl acetate 20:1 to 10:1) to give the corresponding amine **3**.

General Procedure for the Hydrogenative Reductive Amination of Aldehydes

A vial was charged under an argon atmosphere with aldehyde **4** (0.5 mmol), 4-anisidine **2a** or amine **2** (0.75 mmol), $Fe_3(CO)_{12}$ (0.02 mmol), dry toluene (1.0 mL), and a magnetic stirring bar and capped with a septum which was equipped with a needle. The vial was placed in the alloy plate, which was then placed into the pre-dried autoclave. Once sealed, the autoclave was purged 3 times with hydrogen, then pressurized to 50 bar, heated at 65 °C, and stirred for 24 h. The autoclave was cooled to 5 °C, depressurized, the reaction mixture was transferred into a flask, evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: heptane/ethyl acetate 20:1 to 10:1) to give the corresponding amine **5** or **6**.

^1H, and ^{13}C spectra were recorded on Bruker spectrometers AVANCE 300 (^1H: 300.13 MHz, ^{13}C: 75.5 MHz, ^{31}P: 121.5 MHz). The calibration of ^1H and ^{13}C spectra was carried out on solvent signals (δ, $CDCl_3$) = 7.26 and 77.0). Chemical shifts are given in ppm, coupling constants are reported in Hz. Mass spectra were recorded on an AMD 402 spectrometer. Elemental analyses were performed at a Leco CHNS-932. IR spectra were recorded as ATR on a BRUKER ALPHA-P. All manipulations were performed under an argon atmosphere using standard Schlenk techniques.

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Keywords: amines · catalysis · iron · ketones · reductive amination

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