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An Iron Catalyzed Reductive Amination of Aldehydes in Isopropyl Alcohol/Water media as Hydrogen Sources

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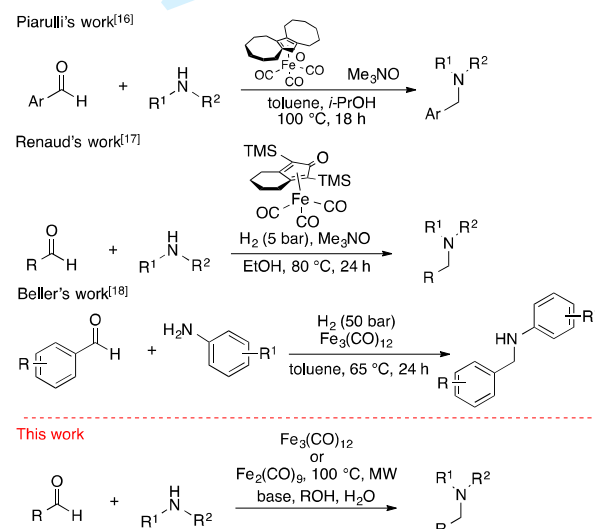
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Abstract. Reductive amination can be carried in *i*-PrOH/H₂O as hydrogen sources using commercially available iron carbonyl complexes. Inside an aqueous alkaline environment, a hydridocarbonyl complex is formed and its reducing potential is exploited for hydrogenation of the imine (or iminium ion) *in situ* obtained from aldehydes or ketones, and primary or secondary amines in almost equimolar ratio. This completely sustainable and hydrogen-free process proceeds at 100 °C using Fe₃(CO)₁₂ as catalyst precursor under convectional heating while Fe₂(CO)₉ gave better results when the reaction was carried out under MW dielectric heating. Either enolizable and not-enolizable aldehydes may be successfully employed in reactions with aliphatic and aromatic amines.

Keywords: amines; iron catalysis; microwave; reduction; hydrides.

Amines represent a wide and important class of organic compounds, present in almost 40% of the registered active pharmaceutical principles (APIs) and in 20% of commercial agrochemicals.^[1] Several synthetic methodologies for their preparation have been described so far, among which reductive amination of carbonyl compounds is the first choice in fine chemical industries, especially when the preparation of secondary and tertiary amines is required.^[2] Reductive amination reactions are based on the formation of an imine (or an iminium ion) intermediate from a carbonyl substrate and a nucleophilic amine followed by a reductive step. The most common reducing agents employed in this step are: (i) metal hydrides as NaBH₄, LiAlH₄ or NaBH₃(OAc) used in stoichiometric amounts,^[3] (ii) molecular hydrogen (often at high pressure) in the presence of homogeneous or heterogeneous noble metal catalysts (*i.e.* Pd, Pt, Rh, Ir)^[4] or (iii) a hydride generated from a hydrogen transfer process catalyzed again by a noble metal.^[5] Although catalytic processes are more sustainable with respect to the

non-catalytic ones,^[6] the use of noble metals as catalysts remain unappealing for industrial and pharmaceutical processes as shown by the limitations introduced by regulatory agencies that requires, for API registration, only small traces (ppm) of noble metals present in final product.^[7] Safer alternatives are represented by "green" metals such as Cu, Fe or Zn catalyst. Recently, Fe catalysis emerged as an appealing field in organic chemistry due to the iron low toxicity, earth abundance and low cost. A number of different iron complexes have been developed to date for the formation of new C-C bond,^[8] for carbonylation^[9] and cycloadditions reactions,^[10] nucleophilic substitutions as well as other transformations recently reviewed.^[11] While iron complexes have been widely explored for the reduction of aldehydes, ketones and imine/iminium ions^[12-14], Fe catalyzed reductive amination has been poorly investigated to date.^[11c,15-18] The research groups of Piarulli,^[16] Renaud^[17] and Beller^[18] recently reported different examples of Fe-catalyzed reductive amination (Scheme 1).

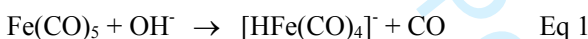


Scheme 1. State of the art.^[16-18]

Tailor made Fe carbonyl complexes in the presence of H₂ gas (Beller's method)^[18] and toluene (a not-ecofriendly solvent, Beller's and Piarulli's methods) are yet required.^[16,18] In addition, these approaches have been almost applied mainly to aromatic amines.^[13,18]

Herein, we present an alternative iron catalyzed and hydrogen free method for the reductive amination of a wide variety of aromatic and aliphatic aldehydes and amines. Contrary to previously reported approaches where Fe is used to activate H₂, we were intrigued by the possibility to employ a transient hydridocarbonyl complex, generated from iron carbonyl complexes in alkaline medium, as the hydrogen source in the reducing step of reductive amination reactions. The formation of carbonylhydridoferrates has been the subject of several studies mainly directed toward their stoichiometric applications in chemical reduction reactions.^[19] Only few reductive processes catalyzed by hydridocarbonyl complex have been described, some of them requiring CO atmosphere (from 1 to 100 atm).^[19a]

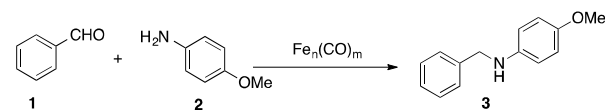
Carbonylhydridoferrate can be easily generated starting from Fe(CO)₅ in alkaline medium as reported in equation 1.^[19a, 20]



Once [HFe(CO)₄]⁻ has obtained, the reductive potential of the carbonylhydridoferrates might be exploited in an iron mediated reductive amination where water (the OH⁻ source) is the hydrogen donor, a sustainable protocol with a potentially high impact on amine synthesis.

We first investigated the possibility to perform a reductive amination using Fe₃(CO)₁₂ as precursor of the hydridodecarbonyl complex. Following our previous experience, the reaction of benzaldehyde with *p*-anisidine was chosen as the model to explore reaction conditions. 2-Propanol (*i*-PrOH) was selected as the solvent as well as the potential hydride source, while an excess of the amine was employed to guarantee the alkaline medium. At first, the reaction was carried out under CO atmosphere in order to stabilize the expected catalytic species (Table 1, entry 1). The choice of Fe₃(CO)₁₂ was based on our previous successful microwave-assisted aminocarbonylation of ynamides.^[9b] In the first attempt, *p*-anisidine **2** was employed as both the reactant and the base, under microwave (MW) irradiation. *i*-PrOH was the solvent under CO atmosphere (6.8 atm) at 100 °C for 20 minutes and using 0.06 equivalents of Fe₃(CO)₁₂. Only a 10% conversion of **2** into product **3** was observed. The presence of oxygen proved to be detrimental for the catalytic process; in fact, an improvement in the yields of **3** was observed when the reaction mixture was degassed before heating (Table 1, entry 2). A substantial increment from 35 to 80% conversion was observed when the reaction was carried out in a sealed tube charged with 1 atm of CO, and heated for 12 h at 100 °C into an oil bath (Table 1, entries 2-3).

Table 1. Optimization of reaction conditions.



En.	Cat. (eq.)	Reaction conditions	Conv ^b
1 ^a	Fe ₃ (CO) ₁₂ (0.06)	CO (6.8 atm), <i>i</i> -PrOH, MW 100 °C, 20 min	10
2 ^{a,c}	Fe ₃ (CO) ₁₂ (0.06)	CO (6.8 atm), <i>i</i> -PrOH, MW 100 °C, 20 min	35
3 ^{a,c}	Fe ₃ (CO) ₁₂ (0.06)	CO (1 atm), <i>i</i> -PrOH, 100 °C, 12 h	80
4 ^{a,c}	Fe ₂ (CO) ₉ (0.06)	CO (1 atm), <i>i</i> -PrOH, 100 °C, 12 h	41
5 ^{a,c}	Fe ₂ (CO) ₉ (0.06)	CO (1 atm), <i>i</i> -PrOH, MW 100 °C, 20 min	88
6 ^{c,d}	Fe ₃ (CO) ₁₂ (0.2)	PPh ₃ (0.4 eq), TEA (0.4 eq), CO (1 atm), <i>i</i> -PrOH, 12 h	32
7 ^{c,d}	Fe ₃ (CO) ₁₂ (0.2)	DMP (0.4 eq), TEA (0.4 eq), CO (1 atm), <i>i</i> -PrOH, 12 h	76
8 ^{c,d}	Fe ₃ (CO) ₁₂ (0.2)	DMAP (0.4 eq), CO (1 atm), <i>i</i> -PrOH, 100 °C, 12 h	78
9 ^{c,d}	Fe ₃ (CO) ₁₂ (0.2)	DMAP (0.2 eq), CO (1 atm), <i>i</i> -PrOH, 12 h	60
10 ^{c,d}	Fe ₃ (CO) ₁₂ (0.2)	DMAP (0.4 eq), <i>i</i> -PrOH, 12 h	89
11 ^{c,d}	Fe ₃ (CO) ₁₂ (0.06)	DMAP (0.4 eq), <i>i</i> -PrOH, 12 h	80
12 ^{c,d}	Fe ₃ (CO) ₁₂ (0.04)	DMAP (0.4 eq), <i>i</i> -PrOH, 12 h	52
13 ^{c,e}	Fe ₃ (CO) ₁₂ (0.04)	NaOH (1 eq), <i>i</i> -PrOH, 12 h	49
14 ^{c,e}	Fe ₃ (CO) ₁₂ (0.06)	NaOH (0.4 eq), <i>i</i> -PrOH, 12 h	45
15 ^{c,e}	Fe ₃ (CO) ₁₂ (0.04)	NaOH (0.4 eq), DMAP (0.4 eq), <i>i</i> -PrOH, 12 h	85
16 ^{c,e}	Fe ₃ (CO) ₁₂ (0.04)	NaOH (0.4 eq), DMAP (0.4 eq), <i>i</i> -PrOH/H ₂ O (10:1), 12 h	95
17 ^{c,e}	Fe ₂ (CO) ₉ (0.06)	NaOH (0.5 eq), DMAP (0.2 eq), <i>i</i> -PrOH/H ₂ O (10:1), MW, 15 min	98

[a] **1** (1 eq), **2** (2 eq), Fe complex 0.06 eq; [b] Conversion determined by GC/MS analysis; [c] The reaction mixture was degassed before irradiation. [d] **1** (1 eq), **2** (1 eq), 100 °C. [e] **1** (1.5 eq), **2** (1 eq), 100 °C.

Interestingly, when Fe₂(CO)₉ was used as Fe source, an opposite behavior was observed. Convective heating (oil bath) led to **3** with 45% conversion while 88% conversion was obtained when **2** was reacted for 1 h at 100 °C under MW dielectric heating (Table 1, entries 4-5).

Starting from these data, we further investigated the reductive amination protocol in the presence of Fe₃(CO)₁₂ or Fe₂(CO)₉ both under convective heating and MW dielectric heating respectively (Table 1, entries 6-17). Different solvents, additives and bases were employed and, in order to make the protocol sustainable and atom economic, the starting aldehyde **1** and the amine **2** were used in equimolar ratio (for additional experiments see Table S1). When

a 1:1 mixture of PPh₃ and TEA in the presence of Fe₃(CO)₁₂ (0.2 eq) and CO (1 atm) was used, the amine **3** was obtained with 32% conversion in *i*-PrOH (Table 1, entry 6). The use of DMAP instead of PPh₃ led to **3** with 76% conversion in *i*-PrOH (Table 1, entry 7). **Additional improvements in the conversion were observed when DMAP was used without TEA as reported in entry 8.** Lowering down the amount of DMAP to less than 0.4 eq, gave the formation of 60% of amine **3** together with a 25% of unreacted imine **5** (Table 1, entry 9). Finally, based to the observation that an increase in the CO pressure did not have any effect on the conversion, a CO-free reaction was investigated. Interestingly, under these conditions, the amine **3** was still formed with 89% conversion (Table 1, entry 10). Thus, additional efforts were undertaken to further optimize the CO-free reaction (Table 1, entries 11-17). With DMAP alone, the amount of Fe₃(CO)₁₂ could not be lowered to less than 6 mol% without a dramatic drop in the conversion (Table 1, entries 11-12). Analogously, replacement of DMAP with NaOH decreased the conversion, even using the higher amount of the iron carbonyl complex (Table 1, entries 13-14). However, with a correct blend of aqueous NaOH and DMAP, a final high conversion of **1** and **2** into amine **3** was observed with both the iron carbonyl complexes (Table 1, entries 15-17). However, a strong link between the iron catalyst used and the heating source exists. In fact, whilst Fe₃(CO)₁₂ worked well under convectional heating (oil bath, 100 °C 12 h), the safer unvolatile^[21] Fe₂(CO)₉ gave excellent conversion only under MW dielectric heating at 100 °C for 10 min. **This different behavior may be related to the different stability interaction with MWs: Fe₃(CO)₁₂ generates local hot spots during MW heating contrary to Fe₂(CO)₉.** The behavior of the two complexes in microwave rotational spectroscopy is also very different,^[22] suggesting a diverse heating profile during MW irradiation. Looking to the electrons exchanged during the red-ox process, the reductive amination requires 2 e⁻ for each imine molecule. As Fe₃(CO)₁₂ may potentially transfer a maximum of 30 e⁻, 1 mole of the metal complex may process a maximum of 15 moles of imine. Thus, a catalytic process should require less than 6.7 mol% of Fe₃(CO)₁₂ or, 9.1 mol% of Fe₂(CO)₉. **Although a complete electron exchange is not plausible, the minimum amount required for high conversion was 4 mol% of Fe₃(CO)₁₂ and 6 mol% of Fe₂(CO)₉, proving that the reaction is not a stoichiometric iron complex reduction.** Optimized conditions for 98% conversion of **1** and **2** (equimolar) into amine **3** were 6 mol% of Fe₂(CO)₉, 0.4 eq of DMAP in *i*-PrOH/water, alkalized with 0.4 eq of NaOH, as solvent and hydride source, at 100 °C for 15 min under MW dielectric heating. **Following these conditions, compound **3** was obtained in comparable yields with respect to Beller's¹⁸ (97% yield) and Piarulli's¹⁶ (99% yield) methods.** The scope of the reaction was finally explored, and the results are summarized in Table 2.

Table 2. Reaction scope.

Entry ^[a]	Carbonyl compd.	Product	Conv. ^[b] (Yield %)
1			98% (93)
2			65% (40)
3			85% (57)
4			99% (95)
5			85% (53)
6			82% (51)
7			87% (80)
8			83% (60)
9			80% (52%)
10			80% (40)
11			90% (65)
12			95% (77)
13			76% (62)
14			81% (69)
15			64% (47)
16			48% (41)
17			53% (39)

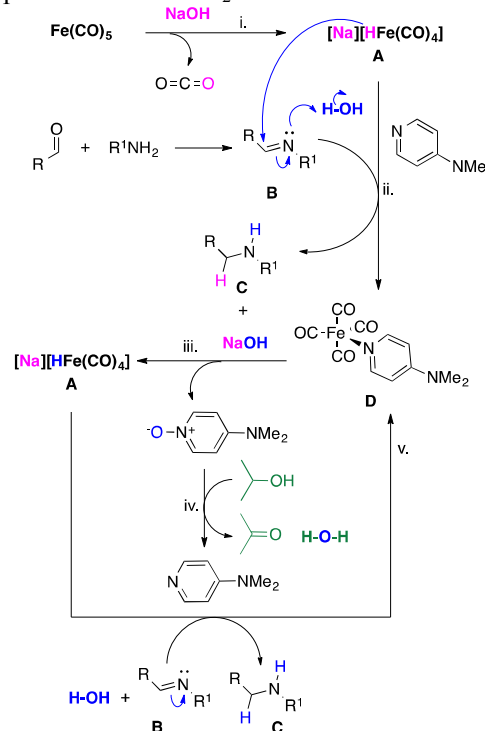
[a] Carbonyl compound (1.5 eq), amine (1 eq), Fe₂(CO)₉ (0.06 eq), NaOH (0.5 eq), DMAP (0.2 eq), *i*-PrOH/H₂O (10:1), MW, 100 °C, 15 min. [b] Conversion was determined by GC/MS analysis while yields are referred to isolated and fully characterized compounds.

Not-enolizable aldehydes (precursors of products **3-11**) gave acceptable to good yields of the corresponding secondary and tertiary amines (Table 2). The only exception was represented by the less nucleophilic *p*-fluoro aniline, although compound **4** was isolated in 40 % yield (Table 2, entry 2). Enolizable aldehydes could be also used in this reaction leading to products **12-14** with good conversions (Table 2, entries 10-12). Particularly, compound **13** was obtained in comparable yields with respect to Renaud's¹⁷ protocol. The reaction conditions are compatible with the presence of a double bond (Table 2, entry 13) and an aqueous solution of formaldehyde can be used for methylation of a primary amine (Table 2, entry 16). Ketones react also although with low conversion/yield (Table 2, entries 15 and 17). As expected, the reaction follows the general trend of reductive amination that occurs with better yields when non-enolizable carbonyl compounds and electronrich aromatic amines were employed. All the reaction in Table 2 were performed using $\text{Fe}_2(\text{CO})_9$ under MW dielectric heating. Reaction yields using $\text{Fe}_3(\text{CO})_{12}$ (0.04 eq) under convectional heating are reported in SI.

Before the proposal of a convincing mechanism, the possibility of a radical process was excluded as the reaction worked well in the presence of radical scavenger BHT. Then, a study on deuterium incorporation was carried out with D_2O and *i*-PrOD₈ (SI). Maximum deuterium incorporation (93%) was observed when both deuterated reagents were employed, while with H_2O and *i*-PrOD₈ a 20% of the deuterated amine was obtained. Although D_2O (or OD⁻) seems to be the major hydride source, *i*-PrOH was oxidized to acetone, identified in the final reaction mixture. On the other hand, DMAP seems to be also required for a high yield reductive amination. Based on these observations, the proposed mechanism is described in Scheme 2. In a first step, the Fe carbonyl and NaOH react generating the acylhydride intermediate **A** with contemporary elimination of a molecule of CO_2 (Step i. in Scheme 1). The active catalyst **A** transfers the hydride ion to the *in situ* formed imine **B** that is immediately protonated by H_2O producing the expected amine **C** and NaOH (Step ii.). Contemporarily, DMAP yields the complex **D** which reacts with NaOH, regenerating **A** and DMAP *N*-oxide (Step iii.). DMAP is finally recycled through a (Fe catalyzed) reduction mediated by *i*-PrOH, thus producing acetone and H_2O (Steps iv. and v.). This mechanism is coherent with the results of deuterium incorporating experiments and with a final red-ox balance recruiting *i*-PrOH as reducing agent (the scheme relative to the mechanism with deuterated reagents is reported in SI).

In conclusion, a sustainable iron catalyzed and hydrogen free protocol for the reductive amination of amines and aldehydes has been developed. This procedure is more sustainable than standard metal catalyzed reductive amination reaction as it counts on

the catalysis of the biocompatible safe iron carbonyl complex with *i*-PrOH/ H_2O .



Scheme 2. Proposed reaction mechanism (exemplified with $\text{Fe}(\text{CO})_5$)

The scope of the reaction is wide, and the protocol may be applied to both aliphatic and aromatic amines as well as to enolizable and not-enolizable aldehydes. Finally, the reaction can be carried out in short reaction times and the products can be isolated after simple filtration on a silica pad.

Experimental Section

General procedure to obtain *N*-(4-methoxyphenyl)benzylamine (3**):** MW dielectric heating. In a MW tube, under N_2 atmosphere and under stirring, $\text{Fe}_2(\text{CO})_9$ (29 mg, 0.08 mmol) is solubilized in a mixture of *i*-PrOH (2.5 ml) and water (0.25 ml). The mixture is degassed by sonication bubbling N_2 for 3 min. NaOH (40 mg, 1 mmol) is added and the mixture left under stirring for 5 minutes. benzaldehyde (212 mg, 2 mmol), *p*-anisidine (246 mg, 2 mmol) and DMAP (49 mg, 0.4 mmol) are added to the reaction mixture. The tube is then inserted in a MW cavity and heated for 15 minutes at 100 °C, using a maximum power of 150 W (max internal pressure set at 250 psi). After cooling, the mixture is diluted with CH_2Cl_2 , dried over dry Na_2SO_4 , filtered and the solvent removed under vacuum. The residue is dissolved into dimethoxyethane (5 mL) and passed through a short path of silica. Evaporation of the solvent gave product **3** (429 mg, 93% yield), m.p. 48-50°C, lit^[23] m.p. 49-50 °C.

Convectional heating: in a sealed tube, under N_2 atmosphere and under stirring, $\text{Fe}_3(\text{CO})_{12}$ (60 mg, 0.12 mmol) is solubilized in a mixture of *i*-PrOH (2.5 ml) and water (0.25 ml). The mixture is degassed by sonication bubbling N_2 for 3 min. NaOH (40 mg, 1 mmol) is added and the mixture left under stirring for 5 minutes. benzaldehyde (212 mg, 3 mmol), *p*-anisidine (246 mg, 2 mmol) and DMAP (49 mg, 0.4 mmol) are added to the

reaction mixture. The reaction mixture is heated under stirring for 12 h at 130 °C (external bath temperature, internal temperature previously determined for these conditions 100 °C). After cooling, the mixture is diluted with CH₂Cl₂, dried over dry Na₂SO₄, filtered and the solvent removed under vacuum. The residue is dissolved into dimethoxyethane (5 mL) and passed through a short path of silica. Evaporation of the solvent gave product **3** (387 mg, 91% yield), m.p. 48–50°C.

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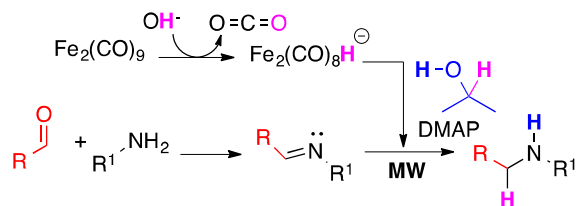
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