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## Hydrogen-free reductive amination using iron pentacarbonyl as a reducing agent†

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**We developed solvent-free reductive amination without an external hydrogen source using iron pentacarbonyl as a reducing agent. Neither a catalyst nor any other additives were employed. Various types of substrates are suitable for the reaction, including those with low reactivity, e.g. benzophenone. Among others, the protocol tolerates bromo-, cyano-, benzyloxy-, pyrimidyl and styryl moieties.**

Selective and step-economical syntheses of complex molecules from starting materials easily available in bulk quantities are highly important from economic and environmental points of view. Such protocols should naturally tolerate a variety of functional groups, so that extra steps of introduction and removal of protective groups can be avoided. Recently, we have developed a series of methods for hydrogen-free reductive addition using carbon monoxide<sup>1</sup> as a reducing agent.<sup>2</sup> Starting from aldehydes or ketones, this approach can lead to various classes of compounds, including amines,<sup>2b</sup> amides, esters,<sup>2e,f</sup> pyrrolidines,<sup>2a</sup> and nitriles.<sup>2f</sup> These transformations are usually highly selective and tolerate the presence of aromatic and aliphatic nitrile groups,<sup>2f</sup> esters,<sup>2c</sup> phenols,<sup>2b</sup> carboxybenzyl (Cbz),<sup>2b</sup> trifluoroacetamido,<sup>2b</sup> *N*-benzyl,<sup>2a</sup> *O*-benzyl,<sup>2d</sup> aromatic fluoro,<sup>2f</sup> chloro-<sup>2d</sup> and bromo-moieties,<sup>2a</sup> cyclopropanes, and even aromatic nitro-groups.<sup>2b</sup> Selectivities of these reductive aminations usually appreciably exceed those of standard reductive agents, such as sodium cyanoborohydride.<sup>2b</sup> The natural limitation for the employment of these methods in a laboratory is the necessity to use a carbon monoxide cylinder.

In this context, we sought to develop a homogeneous alternative with CO in a chemically bound form, e.g. using a metal carbonyl complex as a reductant.<sup>3</sup> From the points of view of both safety and economy, iron pentacarbonyl seemed to be the best choice since elemental impurities of iron in pharmaceutical products are much less stringently regulated by the corresponding authorities (e.g. FDA) than most other d-metals due to lower intrinsic toxicity of iron.<sup>5</sup> Moreover production of iron pentacarbonyl exceeds thousands of tons per year and it is the least expensive metal carbonyl available.<sup>6</sup> Iron tetracarbonyl dihydride is a well-known reducing agent; however, it rapidly decomposes at temperatures above  $-20$  °C.<sup>7</sup> The sodium salt is more stable, but is not commercially available and requires highly basic conditions for the synthesis, which can lead to a narrower substrate scope.<sup>4</sup> Herein, we describe the protocol for reductive amination which employs nothing but starting materials and iron pentacarbonyl. No solvent or external hydrogen source is needed.

We chose morpholine and *p*-tolylaldehyde as model substrates. In light of the fact that iron pentacarbonyl is a liquid, improvement of the environmental profile of the reaction by the use of solvent-free conditions seemed very interesting. Thus, we heated the reaction components at 90 °C for 4 hours and did detect formation of product **1a** (Table 1, entry 1). The temperature influence was found to be important in the range up to 130 °C (Table 1, entries 1–3); at higher temperatures no significant yield variability was found (Table 1, entries 3–6). When the amount of the carbonyl was decreased from three to two equivalents, no significant changes were observed (Table 1, entry 3 vs. 8). If the amount of the carbonyl was further decreased, the yield significantly dropped (Table 1, entry 1 vs. 9–11). When the amount of the starting amine (see ESI†) was increased to three equivalents, the yield increased up to 86% with reaction time of four hours. Based on the works of Hieber the reaction between amines and iron pentacarbonyl gives complicated clusters,<sup>8</sup> so the mechanism reductive amination with iron pentacarbonyl seems to be complicated. The molybdenum hexacarbonyl showed the potential in the reductive amination as well (Table 1, entry 3 vs. 12).

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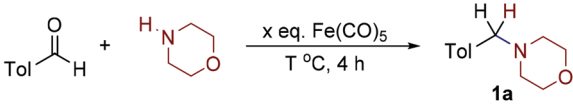
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**Table 1** Investigation of the effects of the amount of iron pentacarbonyl and temperature on reductive amination


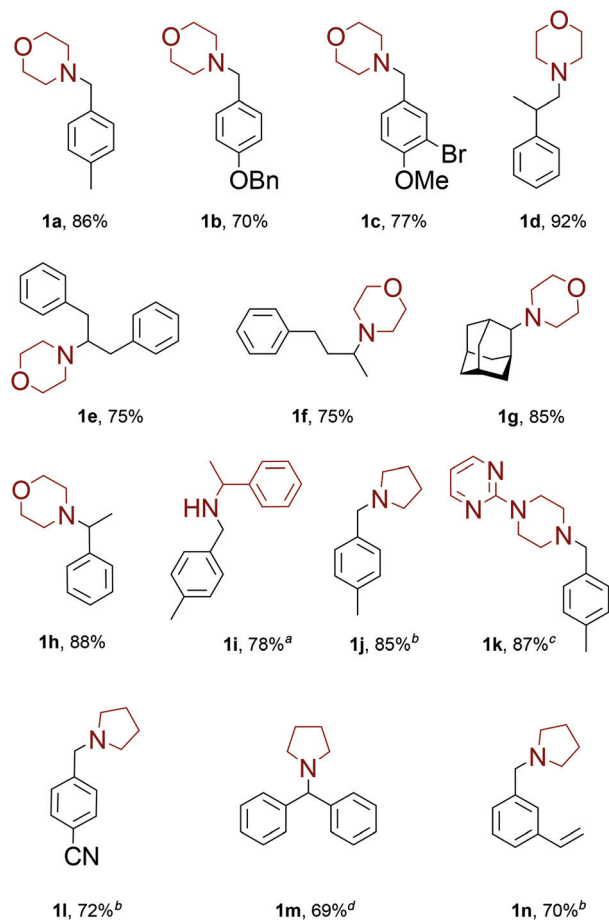
Entry <sup>a</sup>	Fe(CO) <sub>5</sub> , eq.	T, °C	Yield <sup>b</sup> %
1	3	90	14
2	3	110	26
3	3	130	41
4	3	150	40
5	3	160	41
6	3	180	44
7	5	130	51
8	2	130	44
9	1	130	24
10	0.5	130	15
11	0.2	130	11
12 <sup>c</sup>	3	130	25

<sup>a</sup> 0.2 mmol scale. 1.5 eq. of morpholine were used. <sup>b</sup> Yields were determined by GC. Tol = *p*-methylphenyl. <sup>c</sup> Mo(CO)<sub>6</sub> was used instead of Fe(CO)<sub>5</sub>.

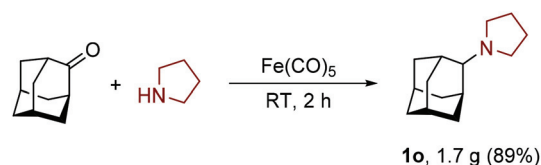
With these results in hand, we proceeded to investigation of the substrate scope of the developed methodology under the optimized reaction conditions (Fig. 1).

A wide range of aldehydes could be successfully employed, including those containing various functional groups prone to reduction by dihydrogen. For example, benzyloxy moiety (**1b**), aromatic bromides (**1c**) and aromatic nitriles (**1l**) can be tolerated. Aliphatic aldehydes are known to undergo self-aldol reaction catalyzed by amines (especially secondary aliphatic amines);<sup>9</sup> however, under our reaction conditions reductive amination product **1d** was isolated in excellent yield. Whereas ketones are usually much less reactive in reductive amination, our methodology worked well with aliphatic ketones **1e–f**. Acetophenone could be converted into product **1h** with isolated yield of 88%. Moreover, even as unreactive ketone as 2-adamantanone **1g** successfully furnished the product in 85% yield. Besides morpholine, other type of tested amines underwent the desired transformation **1i–k** in high yields. The optimum reaction temperature was clearly dependent on the nucleophilicity of the starting amine. For pyrrolidine the reaction proceed well even at room temperature (**1j**, **1l**, **1n**). Other type of amines also could react at room temperature, albeit with lower rate. We were surprised to found that even benzophenone could be successfully employed: after 12 hours at 90 °C product **1m** was isolated in 69% yield. The protocol is so mild that we isolated compound **1n** without any side reactions on the styryl moiety.

The scalability and preparative utility of the developed methodology was exemplified on the synthesis of *N*-adamantylpyrrolidine. Despite the much lower intrinsic reactivity of 2-adamantanone with respect to less sterically challenged substrates, a gram-scale reaction with pyrrolidine proceeded well and furnished product **1n** in 89% yield without the need for any chromatographic isolation (Scheme 1).



**Fig. 1** Studies on the substrate scope. Solvent-free conditions. 3 equivalents of Fe(CO)<sub>5</sub> and amine were employed. 4 h at 130 °C. <sup>a</sup> 2 equivalents of amine were employed. 140 °C. <sup>b</sup> Room temperature. 12 hours. <sup>c</sup> 140 °C. <sup>d</sup> 90 °C. 12 hours.



**Scheme 1** Scaled-up synthesis of *N*-adamantyl-pyrrolidine at room temperature.

In conclusion, we have shown that the concept of hydrogen-free reductive amination can be expanded to metal carbonyls as reducing agents, which can lead to the more selective approaches in organic synthesis. The synthetic value of the developed methodology was demonstrated by efficient preparation of a representative range of amines including clean gram-scale synthesis not requiring chromatographic purification. The reaction proceeds well even in case of poorly reactive ketones such as benzophenone.



## Conflicts of interest

There are no conflicts of interest to declare.

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