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Iron-Catalysed Reductive Amination of Carbonyl Derivatives with *ω*-Amino Fatty Acids to Access Cyclic Amines

Duo Wei[a], Chakkrit Netkaew[a], Victor Carré[a], and Christophe Darcel*[a]

Dedication ((optional))

Abstract: A new efficient method for the reductive amination of carbonyl derivatives with *ω*-amino fatty acids catalysed by an iron complex $Fe(CO)_4$(*IMes*) by means of hydrosilylation was developed. A variety of pyrrolidines, piperidines and azepanes were selectively synthesised in moderate to excellent yields (36 examples, 47-97% isolated yields) with a good functional group tolerance.

The presence of *N*-heterocycles is a characteristic feature in pharmaceutical chemistry, material chemistry, and synthetic organic chemistry.[1] Particularly, cyclic amines (such as pyrrolidines, piperidines and azepanes) are present in a large class of natural products and biologically active molecules.[2] (Figure 1)

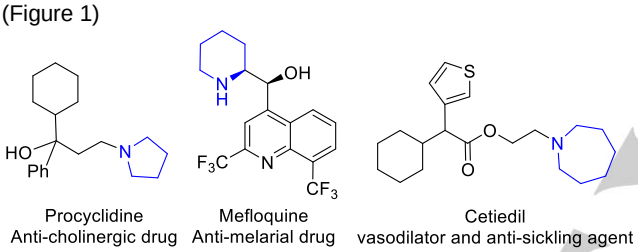
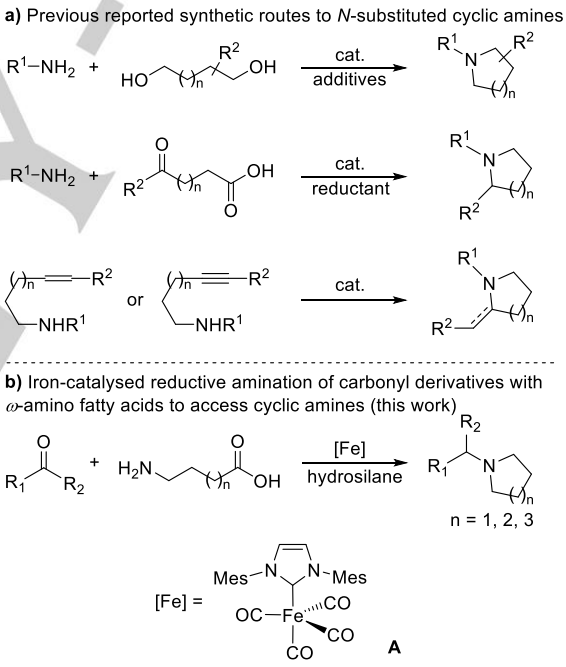


Figure 1. Examples of cyclic amines in drug area

In the past few decades, huge efforts have been devoted to the development of efficient methods for the synthesis of cyclic amines,[3] including hydrogen borrowing,[4] ring-closing metathesis,[5] reductive amination of keto acids (especially levulinic acid)[6] and intramolecular hydroamination reactions[7] (Scheme 1a). In addition, those synthetic routes have been dominated by noble metals as the catalysts, for examples Ir, Ru, Rh and also Pd. In comparison, Earth-abundant metals are relatively less applied in such transformations.

Recently, we have developed an iron-catalysed reductive amination of levulinic acid, 1,5- and 1,6-keto acids leading to pyrrolidines, piperidines and azepanes, respectively, under hydrosilylation conditions.[6c] From a sustainable organic synthesis point of view, iron-catalysed reductive amination of carbonyl derivatives with *ω*-amino fatty acids should be another attractive method to access to *N*-substituted cyclic amine derivatives in one step (Scheme 1b). Indeed, *ω*-amino fatty acids are widely present in plants and animal species: as a representative example, 4-aminobutanoic acid (GABA) is the chief inhibitory neurotransmitter in the mammalian central nervous system and GABA is also sold as a dietary supplement.[8] Furthermore, 5-aminopentanoic acid is a normal metabolite present in human saliva, with a tendency to elevated concentration in patients with chronic periodontitis,[9] and 6-aminohexanoic acid is effective in treatment of certain bleeding disorders (for instance postoperative bleeding), marketed as Amicar.[10]



Scheme 1. a) Representative synthetic routes to *N*-substituted cyclic amines and **b)** Iron-catalysed reductive amination of carbonyl derivatives with *ω*-amino fatty acids (this work).

On the other hand, the last two decades have seen an impressive improvement of the use of iron as a fascinating and valuable alternative transition metal in homogeneous catalysis, more particularly in the reduction areas.[11] For the synthesis of amines, reductive amination is one of most efficient methodologies,[12] in particular with iron catalysts which exhibited good activities.[13] Additionally, reduction *via* hydrosilylation is a promising alternative for the selective catalytic transformation of organic molecules compared to other reduction methods such as the catalytic hydrogenation[14] and transfer hydrogenation reactions,[15] or the stoichiometric reduction with metal hydrides

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(e.g. aluminium and boron hydrides).[16] Thus the use of hydrosilanes is often interesting owing to its operational simplicity, mild conditions and excellent chemoselectivity.[17] Therefore hydrosilanes can be considered as interesting alternative reductants, although siloxane waste is an unavoidable by-product during those procedures.

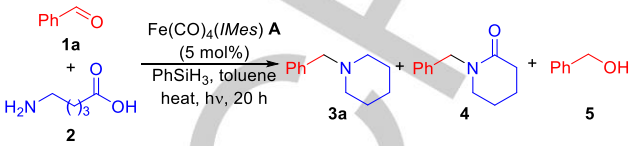
Among the different well-defined iron complexes developed in our group for reduction reactions, $Fe(CO)_4$(*IMes*) **A** [*IMes* = 1,3-bis (2,4,6-trimethylphenyl)imidazol-2-ylidene, Scheme 1b] was efficiently employed as catalyst in the hydrosilylation of esters[18], hydroboration of alkenes[19] and methylation of secondary amines.[20], Additionally, Royo also described for the hydrosilylation of benzaldehyde derivatives using **A** as the catalyst, and Mandal using an abnormal-NHC−$Fe(CO)_4$ succeeded to performed the hydrosilylation of imines with high efficiency.[21]

Herein, we report an iron-catalysed efficient and selective one-pot preparation of *N*-substituted cyclic amines (including pyrrolidines, piperidines and azepanes) *via* reductive amination of carbonyl derivatives with *ω*-amino fatty acids by hydrosilylation (Scheme 1b).

Inspired by recent reports on the preparation of cyclic amines[6] and the application of $Fe(CO)_4$(*IMes*) **A** in reduction area,[20-21] we began our initial optimization work with benzaldehyde **1a**, 5-aminopentanoic acid **2** and phenylsilane in toluene, in the presence of **A** as the catalyst. The preliminary experiment using 5 mol% of **A** associated to 4 equiv. of $PhSiH_3$ at 100 °C upon visible light irradiation (using 24 watt compact fluorescent lamp) showed an interesting result for reductive amination of **1a** and **2**: thus, *N*-benzylpiperidine **3a** was produced in 96% yield (Table 1, entry 1) with only 3% of benzyl alcohol **5** resulting of the reduction of the benzaldehyde, indicating the remarkable selectivity with respect to **3a**.

Afterwards, different hydrosilanes were evaluated in order to study the selectivity of the reaction. Using diphenylsilane (6 equiv.) led to a mixture of 1-benzylpiperidin-2-one (**4**, 59%) and benzyl alcohol (**5**, 40% with no trace amount of the expected piperidine **3a**, entry 2), while with TMDS (1,1,3,3- tetra-methyldisiloxane, 6 equiv.) and PMHS (polymethylhydrosiloxane, 12 equiv.) no reaction occurred (entries 3 and 4). The absence of toluene or visible light irradiation resulted in deteriorative selectivity (entries 5 and 6) as **3a** was obtained in mixture with **4**. Decreasing the temperature to 80 or 50 °C led to a mixture of **3a** and **4** with an increasing amount of **4** (50% and 65%, respectively, entries 7 and 8). Nevertheless, when the reaction was conducted at 30 °C, the conversion was 96% with benzyl alcohol **5** as the major product (64%, entry 9). The quantity of hydrosilanes has also a crucial effect on the selectivity; indeed, increasing the amount of phenylsilane to 5 equiv. or decreasing to 3 and 2 equiv. lowered the selectivity of the reaction (entries 10-12 *vs* 1). Finally, with a lower catalyst loading of **A** (2.5 mol%), a lower conversion (86%) was obtained, with **3a** still being the major product (71%, entry 13). Noticeably, in the absence of catalyst **A** under similar conditions with 2-4 equiv. of phenylsilane, no *N*-benzylpiperidine **3a** was obtained; the main product obtained was the *N*-benzylpiperidinone **4**. Additionally, using $Fe(CO)_5$ or $Fe_3(CO)_{12}$ under our optimized conditions, even if full conversions were observed, benzyl alcohol resulting from the reduction of benzaldehyde was the major product obtained (59 and 99% respectively), showing the crucial role of the IMes ligand for the selectivity of the reaction. It must be also mentioned that this transformation using the catalyst **A** under hydrogenation or hydrogen transfer conditions did not succeed (Table S2).

Table 1. Optimization of the reaction parameters.[a]



Entry	Silane [equiv.]	T [°C]	Conv. [%]	Yield [%] 3a	4	5
1	$PhSiH_3$ [4]	100	99	96	0	3
2	Ph_2SiH_2 [6]	100	99	0	59	40
3	TMDS [6]	100	0	-	-	-
4	PMHS [12]	100	0	-	-	-
5[b]	$PhSiH_3$ [4]	100	98	67	31	0
6[c]	$PhSiH_3$ [4]	100	99	87	12	0
7	$PhSiH_3$ [4]	80	97	47	50	0
8	$PhSiH_3$ [4]	50	97	32	65	0
9	$PhSiH_3$ [4]	30	96	7	25	64
10	$PhSiH_3$ [5]	100	99	84	1	14
11	$PhSiH_3$ [3]	100	99	30	69	0
12	$PhSiH_3$ [2]	100	95	20	71	4
13[d]	$PhSiH_3$ [4]	100	86	71	13	2

[a] General reaction conditions: **A** (5 mol%), **2** (0.5 mmol), **1a** (0.5 mmol), $PhSiH_3$ and toluene (0.5 mL), visible light irradiation (using 24 watt compact fluorescent lamp), 100 °C, 20 h; then hydrolysis (THF/NaOH 2 N). The conversions and yields were determined by ^1H NMR spectroscopy. [b] neat condition. [c] In the absence of visible light irradiation. [d] **A** (2.5 mol%).

With our optimized conditions in hand (5 mol% of **A**, 4 equiv. of $PhSiH_3$, toluene, 100 °C, 20 h, visible light irradiation, Table 1, entry 1), we then explored the substrate scope for the catalysed reductive amination of carbonyl derivatives with *ω*-amino fatty acids into *N*-substituted cyclic amines (Tables 2, 3 and 4). Benzaldehyde, *o- and p*-tolualdehyde were smoothly converted into the corresponding *N*-substituted piperidines in 92-95% isolated yields (**3a**-**3c**, Table 2). Starting from the hindered mesitaldehyde, the corresponding product **3d** was isolated in good yield (80%). The reactions of *p*-methoxy or *p*-*N*,*N*-dimethyl benzaldehyde afforded the corresponding piperidines **3e**-**3f** in 93 and 63% yields, respectively.

The reaction also tolerated halides giving **3g**-**3i** in 93-95% yields. Notably, piperidines bearing reducible functional groups such as carboxylic ester (**3j**) and amide (**3k**), were prepared in 62 and 78% yields, respectively highlighting the good group tolerance of this transformation. The reaction with *p*-(acetyl)aniline led to a less selective reaction as 72% of the piperidine **3l** was obtained in mixture with 20% of the fully reduced product, 1-((*p*-piperidylmethyl)phenyl)ethan-1-ol. Additionally, hetero-aromatic aldehydes based on pyrrole, furan, thiophene and quinoline cores were effectively transformed to **3m**-**3p** in yields up to 97%. Ferrocene substituent was also tolerated as **3q** was isolated in 89%. Interestingly, starting from isophthalaldehyde, the corresponding dipiperidine derivative **3r**

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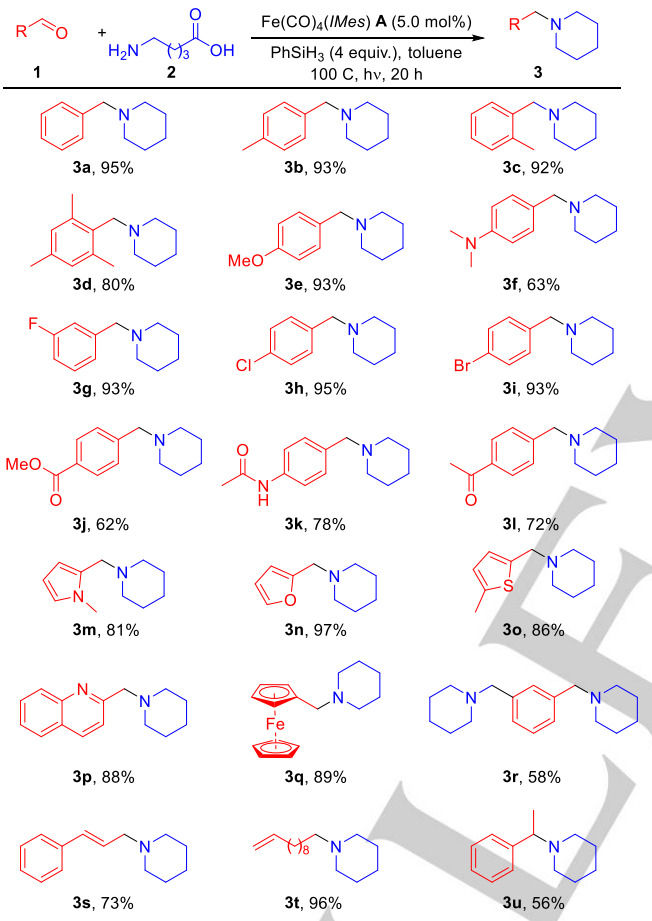
can be purified in moderated yield (58%). When *α,β*-unsaturated aldehyde such as cinnamaldehyde was used, *N*-cinnamylpiperidine **3s** was obtained in 73% isolated yield. Furthermore, linear aldehyde such as 10-undecenal reacted selectively leading to the piperidine **3t** in 96% yield without hydrosilylation of the terminal C=C bond, exhibiting the good functional tolerance towards conjugated or remoted C=C bonds. Noticeably, the reaction can be also conducted with acetophenone, although moderate yield was achieved (**3u**, 56%).

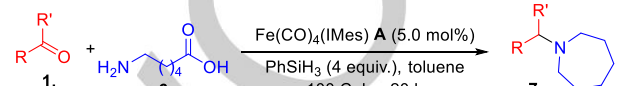
Table 2. Scope of the synthesis of piperidines by reductive amination of carbonyl derivatives with 5-aminopentanoic acid.[a]

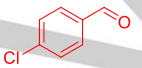
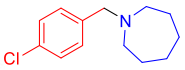
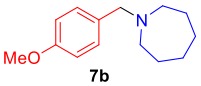
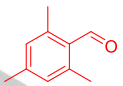
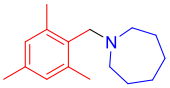
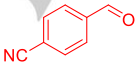
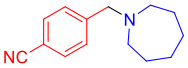
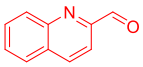
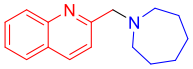
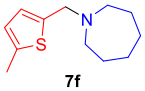
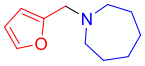
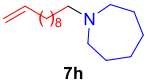
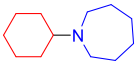
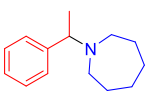


[a] General reaction conditions: **A** (5 mol%), **2** (0.5 mmol), **1** (0.5 mmol), $PhSiH_3$ (4 equiv.) and toluene (0.5 mL), visible light irradiation, 100 °C, 20 h; then hydrolysis (THF/NaOH 2 N). Isolated yields of **3** are shown.

Next, the reductive amination of carbonyl derivatives reaction was extended to 6-aminohexanoic acid **6,** in order to synthesise azepanes (Table 3). In the selected examples depicted in Table 3, *p*-chloro and *p*-methoxy substituted benzaldehydes afforded the corresponding azepanes in 95% and 90% yields, respectively. The steric hindrance did not inhibit the transformation as the product **7c** derived from mesitaldehyde can be isolated in 75% yield. Cyano reducible functional group was tolerated and **7d** was isolated in 82% yield. Heteroaromatic aldehydes based on quinoline, thiophene and furan cores were effectively transformed to **7e**-**7g** in yields up to 95%. Remoted C=C group was not hydrosilylated and **7h** was isolated in 94% yield. Ketones are also appropriate partners in the preparation of azepanes. Indeed, cyclohexanone and acetophenone led to the corresponding azepanes **7i** and **7j** in 87% and 47% yields.

Table 3. Scope of the synthesis of azepanes by reductive amination of carbonyl derivatives with 6-aminohexanoic acid.[a]



Entry	substrate **1**	Product **7**	Yield [%]
1		 **7a**	95
2		 **7b**	90
3		 **7c**	75
4		 **7d**	82
5		 **7e**	91
6		 **7f**	93
7		 **7g**	95
8		 **7h**	94
9		 **7i**	87
10		 **7j**	47

[a] General reaction conditions: **A** (5 mol%), **6** (0.5 mmol), **1** (0.5 mmol), $PhSiH_3$ (4 equiv.) and toluene (0.5 mL), visible light irradiation, 100 °C, 20 h; then hydrolysis (THF/NaOH 2 N). Isolated yields of **7** are shown.

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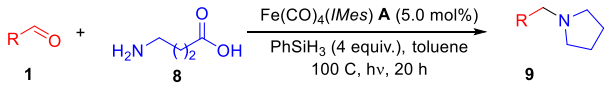
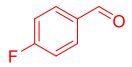
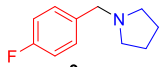
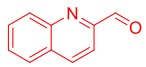
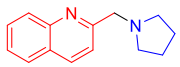
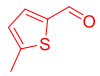
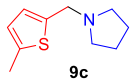
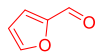
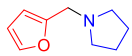
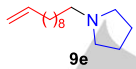
Finally, to show the generality of this cyclic amine preparation, 4-aminobutanoic acid (**8**, GABA) was employed with different aldehydes to prepare pyrrolidines **9** as shown in Table 4. Thus, *p*-fluorobenzaldehyde furnished **9a** in 93% yield. Heteroaromatic aldehydes containing quinoline, thiophene and furan groups can be effectively transformed to **9b**-**9d** in good yields (87-90%). Similar to piperidine **3t** and azepane **7h**, pyrrolidine **9e** was prepared in 95% yield starting from 10-undecenal and **8**, again without alteration of the C=C bond. Even though this method is quite general for the synthesis of 5, 6 and 7 membered cyclic amines, the reaction of *β*-alanine with benzaldehyde did not furnish the desired azetidine product, but the 3-(*N*-benzylamino)propanoic acid was the sole product obtained with 83% NMR yield. (see supporting information, Scheme S3).

Table 4. Scope of the synthesis of pyrrolidines by reductive amination of aldehydes with 4-aminobutanoic acid.[a]



1 + 8 → 9

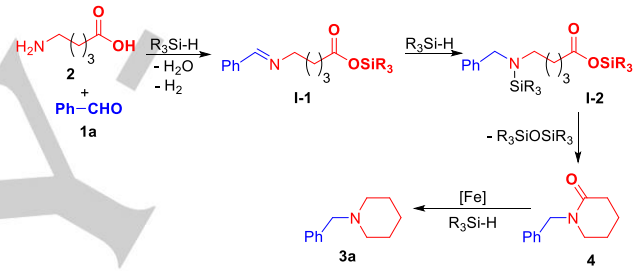
Entry	substrate **1**	Product **9**	Yield [%]
1		 **9a**	93
2		 **9b**	87
3		 **9c**	89
4		 **9d**	90
5		 **9e**	95

[a] General reaction conditions: **A** (5 mol%), **8** (0.5 mmol), **1** (0.5 mmol), $PhSiH_3$ (4 equiv.) and toluene (0.5 mL), visible light irradiation, 100 °C, 20 h; then hydrolysis (THF/NaOH 2 N). Isolated yields of **9** are shown.

Summarising the results described above, cyclic amines can be formed efficiently by the iron catalysed hydrosilylation of *ω*-amino fatty acids in the presence of aldehydes. Importantly, it was shown that the first steps of the transformation generating specifically piperidinone **4** (*i.e.* imine formation, its reduction then transamidation) can be performed in the absence of iron catalyst (see table S1). This transformation seems to be specific to *ω*-amino fatty acids used as with methyl 4-aminobutyric ester, no reduction reaction occurred. Noticeably, carboxylic acids seem to promote the formation of imines in the presence of hydrosilanes (Schemes S2).[22-24] Additionally, the reduction of piperidinones with phenylsilane can be performed only in the presence of iron catalyst.

On another hand, to have information on the nature of the iron active species, a reductive amination of **1a** with **2** using 5 mol% of **A** in the presence of 4 equiv. of $PhSiH_3$ was conducted in a Young NMR tube with visible light irradiation. Noticeably, the signal of H_2 and Fe-H species were observed at 4.46 ppm and –9.13 ppm, respectively, after 3 h of reaction at 100 °C (Figure S1 and S2). The Fe-H signal is very close to the one observed in hydrosilylation of esters.[18]

Based on these observations and on the previous reaction proposed pathways,[2c,6] an imine intermediate **I-1** is first produced by condensation of **1a** with **2** and dehydrogenative silylation of the carboxylic acid moiety with phenylsilane, then generating H_2. The reduction of the imine moiety of **I-1** under hydrosilylation conditions generated the silylamine intermediate **I-2**, then the piperidinone **4** *via* intramolecular transamidation (Scheme 2). The final step is an iron-catalyzed reduction of **4** into **3a** under hydrosilylation conditions.[18,25]



Scheme 2. Possible reaction pathway.

In summary, this contribution described an unprecedented efficient method for the preparation of *N*-substituted cyclic amines (including pyrrolidines, piperidines and azepanes) starting from *ω*-amino fatty acids and a variety of carbonyl derivatives, *via* reductive amination. The reaction proceeds with a high functional group tolerance as reducible groups such as carboxylic ester, amide, cyano and even acetyl, are well tolerated. The notable features of this protocol include the use of an Earth-abundant, nontoxic metal iron complex bearing a *N*-heterocyclic carbene (NHC) ligand as the catalyst (5 mol%) in the presence of phenylsilane (4 equiv.) as the reducing agent at 100 °C and visible-light activation of the catalyst.

Experimental Section

Typical procedure for catalytic reductive amination of carbonyl derivatives with *ω*-amino fatty acids

A 20 mL Schlenk tube was charged with [Fe(CO)$_4$(*IMes*)] **A** (5 mol%), *ω*-amino fatty acids **2**, **6** or **8** (0.5 mmol), aldehyde **1** (0.5 mmol), $PhSiH_3$ (4 equiv.) and toluene (0.5 mL) under the argon atmosphere in this order. Then the reaction mixture was stirred upon visible light irradiation (using 24 watt compact fluorescent lamp) at 100 °C for 20 h. After cooling to room temperature, the reaction was quenched by adding 2 mL THF and 2 mL NaOH (aq.) 2 N, stirred for 2 h at room temperature and then extracted

with 3×2 mL of ethyl acetate. The combined organic fractions were dried over anhydrous Na_2SO_4 for 0.5 h. After filtrate through degreasing cotton, the crude mixture was dried under reduced pressure. The residue was then purified by silica gel column chromatography using a mixture of heptane/ethyl acetate (60:1 to 5:1) as the eluent to afford the desired product.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: iron catalysis • reductive amination • *ω*-amino fatty acids • cyclic amines • hydrosilylation

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[22] Noticeably, the reaction of *p*-methoxybenzylidenebenzimide with 2 equiv. of phenylsilane in toluene at 100 °C for 4 h led to only 14% of (*p*-methoxybenzylphenylamine. The same reaction in the presence of 1 equiv. of acetic acid led to 51% of the resulting amine. (see Scheme S1)

[23] The reductive amination reaction of benzaldehyde with butylamine in the presence of 2 equiv. of phenylsilane and 1 equiv. of carboxylic acid (acetic or valeric) led to the imine as the major product (70-75% yields) with dibenzylbutylamine and N-benzyl-N-butylcarbamides as the by-products whereas without carboxylic acid, only the imine was obtained. (see scheme S2)

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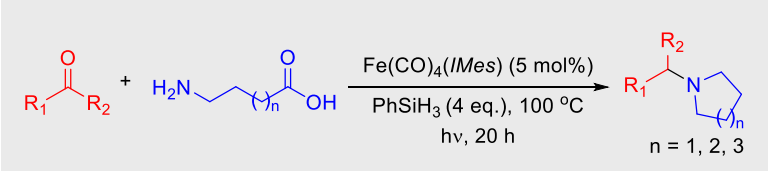

An unprecedented efficient method for the reductive amination of carbonyl derivatives with *ω*-amino fatty acids catalysed by an iron complex was developed. A variety of pyrrolidines, piperidines, azepanes were synthesised in 47-97% isolated yields (36 examples).

*Duo Wei, Chakkrit Netkaew, Victor Carré, and Christophe Darcel**

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Iron-Catalysed Reductive Amination of Carbonyl Derivatives with *ω*-Amino Fatty Acids to Access Cyclic Amines