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# Iron-catalyzed Hydrosilylation of Secondary Carboxamides: Chemoselective Access to Aldimines

Jiajun Wu<sup>+, [a]</sup>, Subash Nethaji Narayanasamy<sup>+, [a]</sup> and Christophe Darcel<sup>\*[a]</sup>

This contribution described the chemoselective reduction of secondary carboxamides to aldimines. To perform such challenging transformation, we reported a catalyzed hydrosilylation using  $\text{Fe}(\text{CO})_4(\text{IMes})$  [IMes = 1,3-bis(2,4,6-trimethylphenyl) imi-

dazol-2-ylidene] as the catalyst, diphenylsilane as the reductant under UV irradiation (350 nm) at room temperature for 16 h. Aldimines were then obtained, after a basic quench, in 32–83% isolated yields. This transformation was unprecedented at iron.

## Introduction

The development of new and improved methods for the preparation of nitrogen based derivatives such as imines, is still a topical and significant area of research in academic centers and the chemical industry.<sup>[1]</sup> Indeed, imines and their derivatives have long been recognized as key intermediates for the synthesis of nitrogen heterocycles, notably as a representative example in alkaloid synthesis (Figure 1).<sup>[2a]</sup> Additionally, Schiff bases bearing imine moiety also exhibited numerous potent anti-microbial, anti-malarial or anti-bacterial activities.<sup>[2b–e]</sup>

Among the various methods available for the synthesis of imines,<sup>[3]</sup> the chemoselective reduction of carboxamides represents a direct and valuable methodology. In this area, the selectivity could be seen as one of the most challenging topics among carboxylic derivatives, owing to (i) the high stability of carboxamides making them less reactive with hydride species,<sup>[4]</sup> the most common metallic hydride reagents used being aluminium and boron hydride reagents,<sup>[5]</sup> (ii) the chemoselective issues (C–O vs C–N bond cleavages), and (iii) the possibility of performing over reductions, thus leading to amines. Additionally, several drawbacks of such stoichiometric metallic reagents can be associated to their uses like their air- and moisture sensibility, and the associated limited substrate scopes due to the lack of functional group tolerance. Nevertheless, during the last two decades, developments of reductive deoxygenation of carboxamides have been achieved for the efficient formation of amines based on transition metal catalytic systems, notably using hydrosilylation conditions.<sup>[6]</sup> In this latter

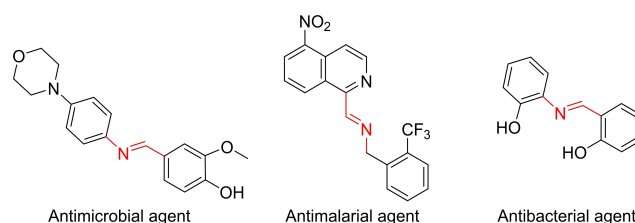
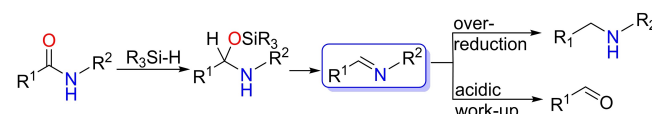


Figure 1. Representative examples of imines with biological activities.

area, iron, as one of the most abundant, inexpensive and environmentally friendly transition metals on earth,<sup>[7]</sup> has gained increasing interests as a potential substitute for the precious ones. Notably, its use in catalytic reductions of carboxylic derivatives has been described via hydrogenation,<sup>[8]</sup> hydrogen transfer<sup>[9]</sup> and hydrosilylation reactions.<sup>[10]</sup> Thus, with the use of promising iron salts or complexes,<sup>[11]</sup> the first selective reduction of carboxamides to their corresponding amines via deoxygenation were developed impressively under hydrosilylation conditions.<sup>[11,12]</sup>

On the other hand, the selective reduction of secondary amides can be regarded as one of the most challenging one, mainly when the imine formation is desired. Indeed, after an initial formation of the imine intermediate, a further easier reduction can take place giving finally to the corresponding secondary amines or its acidic hydrolysis thus leading to aldehydes.<sup>[13]</sup> (Scheme 1)

In terms of the efficient synthesis of imines from carboxamides, one of the first report mentioning such preparation under hydrosilylation conditions was disclosed in 2010 by Charette and co-workers. They described a general and chemoselective method for the reduction of secondary amides leading to aldimines, using 1.05 equiv. of triflic anhydride in association with stoichiometric amount of 2-fluoropyridine and  $\text{Et}_3\text{SiH}$  as the reductant, after a basic work-up.<sup>[13c]</sup> Even if exhibited a very



Scheme 1. Selectivity in reduction of secondary carboxamides.

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good functional tolerance, the reaction had to be conducted at  $-78^{\circ}\text{C}$ . This transformation can also be successfully conducted using transition metal catalysis. In 2012, Brookhart reported such transformation using 0.1 mol% of  $[\text{Ir}(\text{COE})_2\text{Cl}]_2$  (COE = cyclooctene) in the presence of 2 equiv. of diethylsilane at room temperature for 0.2–5 h.<sup>[14]</sup> Very recently, Cantat *et al.* performed the reaction with 10 mol% of the Schwartz's reagent ( $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$ ) in the presence of 2.1 equiv. of  $(\text{EtO})_3\text{SiH}$  at  $80^{\circ}\text{C}$  for 16 h.<sup>[15]</sup> (Scheme 2)

Based on our recent contributions involving iron-catalyzed reduction of polar unsaturated derivatives,<sup>[16]</sup> especially performing reactions under milder conditions, and cascade reductive formation of cyclic amines,<sup>[17]</sup> the above scarce examples of selective reductions of secondary carboxamides to aldimines encouraged us to investigate this transformation using NHC-iron (0) complex **Cat1** under hydrosilylation conditions. Indeed, to the best of our knowledge, this is the first report dealing with the selective reduction of secondary amides to imines at iron.

## Results and Discussion

Initially, to start our investigation, N-benzylbenzamide **1a** was chosen as the substrate model and the reaction was conducted in the presence of 5 mol% of  $\text{Fe}(\text{CO})_4(\text{IMes})$  **Cat1** [IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene] upon the UV-light irradiation at 350 nm at room temperature. When performing the reaction with 2 equiv. of diethylsilane in toluene for 6 h, **2a** was selectively obtained in 66% yield, meanwhile the over-reduced secondary amine **3a** was also detected in 10% yield (Table 1, Entry 1). In order to acquire the highest selectivity, the nature of the hydrosilane was then evaluated. Delightfully, secondary silanes (e.g.  $\text{PhMeSiH}_2$ ,  $\text{Ph}_2\text{SiH}_2$ ) exhibited better performances than tertiary ones (e.g. 1,1,3,3-tetramethyldisiloxane (TMDS), triethoxysilane and triethylsilane), with which no conversion was detected (entries 1–3 vs 4–6). Remarkably, diphenylsilane was also able to reduce **1a**, affording to the desired aldimine **2a** in 63% yield, notably without production of amine **3a**. Noticeably, the use of primary silane, phenylsilane, led to a mixture of **2a** and **3a** in 30% and 68% yields, respectively, after 16 h of reaction. (Entries 7 and 8) The ensuing solvent variation study identified THF as the best reaction medium for the given reduction (Table 1, entries 9–14 and Table S1). Poor result was obtained when conducting the

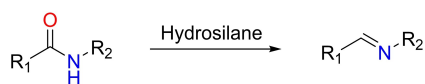
reaction in non-polar cyclohexane (21% yield, entry 9). The reaction in more polar solvent gave better activities. Thus, in dichloromethane, **1a** led to **2a** in a moderate yield (61%), but with a small amount of **3a** (4%, entry 10). Thereafter, oxygenated solvents (e.g. tetrahydrofuran (THF), diethyl ether and methyl *tert*-butyl ether (MTBE)) were evaluated and provided similar results for the selective formation of **2a** (54–70%, entries 11–14).

It should be underlined that performing the reaction with prolonged time is crucial in order to further improve the efficiency of the reduction, as the reaction of **1a** with 2 equiv. of diphenylsilane in THF for 9 h led to **2a** in 81% (Entry 15). Noticeably, decreasing the quantity of diphenylsilane to 1.2 equiv. had a deleterious effect on the reactivity as the imine **2a** was obtained in only 30% even after a prolonged reaction time (15 h, entry 16). Furthermore, increasing the loading of diphenylsilane to 2.5 equiv. has a beneficial effect on the efficiency with the yield of **2a** reaching 95% (entry 17).

Noticeably, in the absence of catalyst **Cat 1**, no reaction occurred, and when performing the reaction with 5 mol% of the commercially available  $\text{Fe}(\text{CO})_5$ , the imine **2a** was detected in only 3%. (Entries 18 and 19) Finally, using the in situ generated IMes ligand, without additional iron species, no reaction took place. (Entry 20) These results demonstrate the superior activity of the **Cat 1** thanks to the synergic association of both IMes and iron carbonyl moieties. Importantly, the role of the UV activation (350 nm) was also shown as no reaction was observed when conducted the transformation in absence of UV irradiation, even if heating at  $100^{\circ}\text{C}$  for 16 h. (Entry 21)

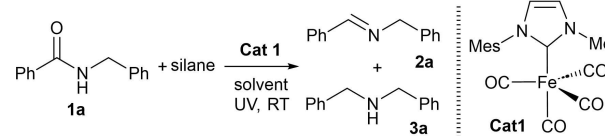
With the optimized reaction conditions [2.5 equiv. of diphenylsilane, 5 mol% of **Cat 1**, in THF at room temperature under UV-light irradiation (350 nm)] in hand (Table 1, Entry 17), the scope and limitation of this selective reduction reaction was then evaluated (Scheme 3). N-benzylbenzamide **1a** led to the corresponding imine **2a** in 95% NMR yield and 78% isolated yield, after purification by chromatography on basic alumina. Similarly, N-cyclohexylbenzamide **1b** were selectively reduced to imine **2b** in in 90% NMR yield and 74% isolated yield. The hydrosilylation of N-cyclohexyl-benzamides decorated with electron donating methoxy or methyl group at *para*-position led to the corresponding imines **2c** and **2d** in 68% isolated yields. Notably, the reaction proceeded efficiently with *o*-, *m*-substituted N-cyclohexyltoluamides, even if the *ortho*-substituted one led to lower NMR-Yield (**2f**, 71%). Starting from *o*-, *m*- and *p*-substituted halogenated N-cyclohexyl-benzamides, the corresponding imines **2g–2k** were obtained in 67–94% NMR yields and up to 80% isolated yields, showing that fluoro, chloro, bromo and even iodo groups can be tolerated. N-cyclohexylbenzamide bearing a strong electron withdrawing group such as trifluoromethyl in *para* position was also selectively reduced giving the imine **2l** in 78% isolated yield.

N-benzyl benzamide bearing electron donating on both aryl moieties were also reduced leading to the corresponding imine **2z** in 89% NMR yield. The scope of the reaction with respect to the nitrogen substituents was then explored. N-alkyl substituted benzamides including cyclohexylmethyl, dodecyl, and *tert*-butyl



Charette (2010) $\text{Ti}_2\text{O}$ (1.05 equiv.), $\text{Et}_3\text{SiH}$ (1.1 equiv.), 2-F-pyridine (1.1 equiv.), $-78^{\circ}\text{C}$ to rt, then basic work-up	Brookhart (2012) $[\text{Ir}(\text{COE})_2\text{Cl}]_2$ (0.1 mol%), $\text{Et}_2\text{SiH}_2$ (2 equiv.), RT, 0.2–5 h	Cantat (2022) $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$ (10 mol%), $(\text{EtO})_3\text{SiH}$ (2.1 equiv.), $80^{\circ}\text{C}$ , 16 h
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**Scheme 2.** Selective reduction of secondary carboxamides to aldimines under hydrosilylation conditions.

**Table 1.** Optimization conditions for the formation of the imine **2a**<sup>[a]</sup>


Entry	Silane (equiv.)	Solvent	Time (h)	Yield of <b>2a</b> (%) <sup>[b]</sup>	Yield of <b>3a</b> (%) <sup>[b]</sup>
1	Et <sub>3</sub> SiH <sub>2</sub> (2)	Toluene	6	66	10
2	PhMeSiH <sub>2</sub> (2)	Toluene	6	25	0
3	Ph <sub>2</sub> SiH <sub>2</sub> (2)	Toluene	6	63	0
4	TMDS (2)	Toluene	6	0	0
5	(EtO) <sub>3</sub> SiH (2)	Toluene	6	0	0
6	Et <sub>3</sub> SiH (2)	Toluene	6	0	0
7	PhSiH <sub>3</sub> (2)	Toluene	6	27	18
8	PhSiH <sub>3</sub> (2.5)	Toluene	16	30	68
9	Ph <sub>2</sub> SiH <sub>2</sub> (2)	Cyclohexane	6	21	0
10	Ph <sub>2</sub> SiH <sub>2</sub> (2)	CH <sub>2</sub> Cl <sub>2</sub>	6	61	4
11	Ph <sub>2</sub> SiH <sub>2</sub> (2)	Me-THF	6	54	0
12	Ph <sub>2</sub> SiH <sub>2</sub> (2)	THF	6	68	0
13	Ph <sub>2</sub> SiH <sub>2</sub> (2)	Et <sub>2</sub> O	6	70	0
14	Ph <sub>2</sub> SiH <sub>2</sub> (2)	MTBE	6	69	0
15	Ph <sub>2</sub> SiH <sub>2</sub> (2)	THF	9	81	2
16	Ph <sub>2</sub> SiH <sub>2</sub> (1.2)	THF	15	30	0
17	Ph <sub>2</sub> SiH <sub>2</sub> (2.5)	THF	9	<b>95</b>	3
18 <sup>[c]</sup>	Ph <sub>2</sub> SiH <sub>2</sub> (2.5)	THF	16	0	0
19 <sup>[d]</sup>	Ph <sub>2</sub> SiH <sub>2</sub> (2.5)	THF	16	3	0
20 <sup>[e]</sup>	Ph <sub>2</sub> SiH <sub>2</sub> (2.5)	THF	16	0	0
21 <sup>[f]</sup>	Ph <sub>2</sub> SiH <sub>2</sub> (2.5)	THF	16	0	0

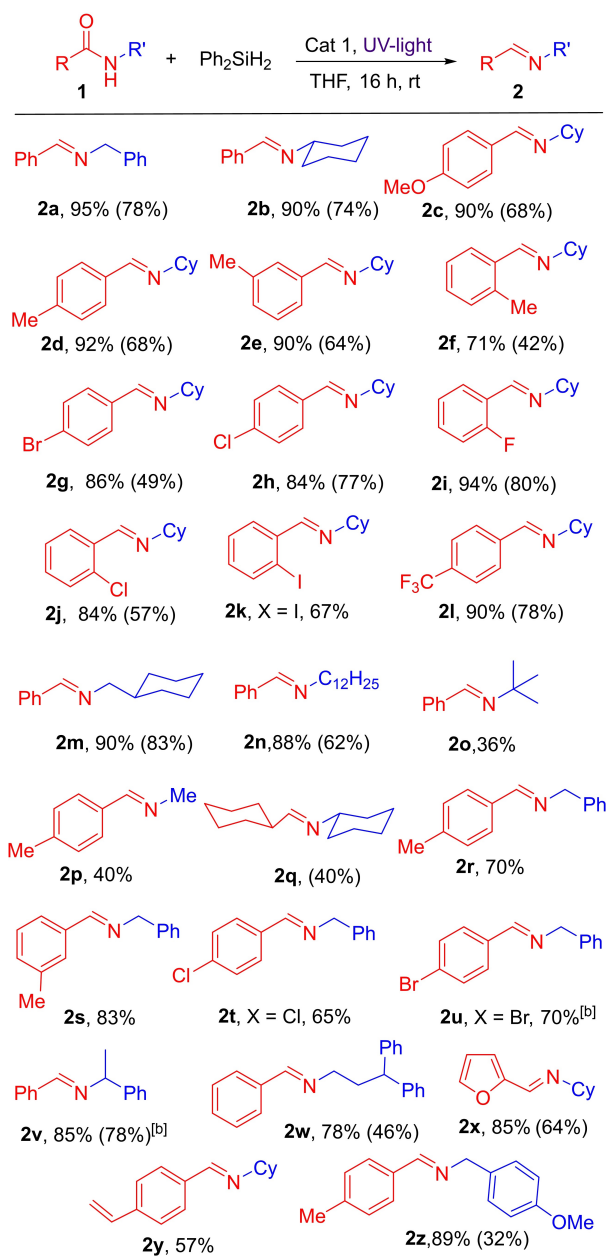
[a] Reaction conditions: N-benzylbenzamide **1a** (0.2 mmol), hydrosilane (2–2.5 equiv.), Fe(CO)<sub>4</sub>(IMes) **Cat 1** (5 mol%), solvent (0.2 mL), upon the UV-light irradiation (350 nm) under argon, for 6–16 h at room temperature; The reaction was then quench with 5 mL of saturated aqueous solution of NaHCO<sub>3</sub>. [b] Yields were determined by <sup>1</sup>H NMR using dibromomethane as internal standard. [c] The reaction was performed without catalyst **Cat 1**. [d] 5 mol% of Fe(CO)<sub>5</sub> was used instead of **Cat 1**. [e] 5 mol% of the NHC ligand IMes, prepared from the corresponding imidazolium chloride salt by deprotonation with *t*-BuOK was used instead of **Cat1**. [f] Reaction performed in the absence of UV light at 100 °C.

were reduced smoothly to lead to **2m–p** in 36–90% NMR yields.

Additionally, the reduction of N-cyclohexyl-cyclohexylamine was also conducted under standard conditions, yielding the imine **2q** in 40% isolated yield. Noticeably, even if the purifications of the obtained N-benzylimines were more tedious by chromatography on basic alumina in our hands, the hydrosilylation of N-benzylbenzamides can be performed conducting to the N-benzylimines in 65–83% NMR yields. Interestingly, the reaction can be performed with N-1-phenylethylbenzamide and N-(3,3-diphenylpropyl) benzamide, and the corresponding imines **2v** and **2w** were isolated in 78% and 46%, respectively. Heterocycle substituent such as furyl was also tolerated during this reduction, as illustrated in the preparation of N-cyclohexyl-2-furylmethylideneimine **2x** in 64% isolated yield. C=C bond were also tolerated as demonstrated with the reduction of N-cyclohexyl-4-vinylbenzamide leading to the corresponding imine **2y** (57% NMR yield).

It should be mentioned that under such conditions, N-cyclohexyl 3-(2-thienyl) prop-2-enamide could not be reduced, showing that conjugated C=C bond seems to inhibited the transformation. Additionally, no reaction took place with N-arylbenzamide such as N-phenylbenzamide, N-(*p*-tolyl) benzamide and *p*-cyanophenylbenzamide. Noticeably, when performing the reaction as N-phenylbenzamide using diethylsilane for 48 h, less than 10% conversion was detected. (see SI, Scheme S1)

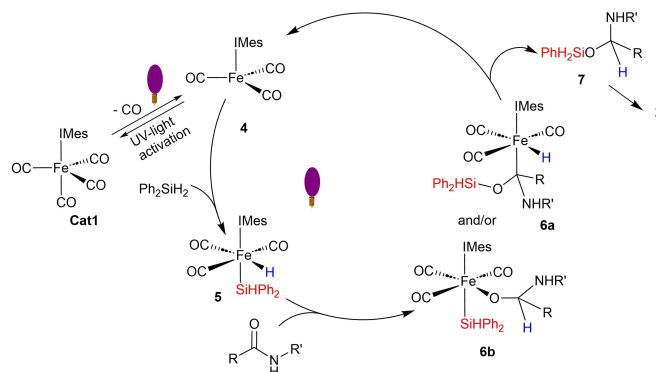
During this study, we aimed to gain further insights into the mechanism thanks to a series of stoichiometric experiments. We have already shown that Fe(CO)<sub>4</sub>(IMes) **Cat1** was able to generate a 16 e<sup>-</sup> iron(0) catalytic species **4** upon the UV-light irradiation at rt, via a non reductive elimination of a CO ligand. **4** is then able to promote the oxidative addition of hydrosilane generating iron hydride silyl species **5**.<sup>[15,16]</sup> Noticeably, similar complexes to the intermediate **5** was isolated and fully characterized including by X-ray analysis.<sup>[18]</sup> The active role of



**Scheme 3.** Scope of the iron-catalyzed selective reduction of secondary amides.<sup>[a]</sup> [a] Reaction conditions: Secondary amides **1** (0.5 mmol, 1 equiv.), diphenylsilane (1.25 mmol, 2.5 equiv.), **Cat 1** (5 mol%), THF (0.5 mL) upon the UV-light irradiation (350 nm) at room temperature for 16 h under argon; Yields were determined by <sup>1</sup>H NMR using dibromomethane as the internal standard; Isolated yields were given in parentheses; The reaction was then quenched with 5 mL of saturated aqueous solution of NaHCO<sub>3</sub>. [b] 48 h.

UV can be rationalized analyzing the UV-Vis spectrum of **Cat 1** in THF exhibiting a large absorption band centered at 278 nm. (See SI, Figure S1)

We also performed a light on/off experiment for the reaction of **1a** with 2.5 equiv. of Ph<sub>2</sub>SiH<sub>2</sub> in the presence of 5 mol% of **Cat 1** under the standard reaction conditions. Interestingly, it showed that the reaction almost stopped in dark, and restarted as soon as exposed to UV irradiation. These observations gave a clear indication that UV is not only



**Scheme 4.** Proposed mechanism for the selective reduction of secondary carboxamides to aldimines

mandatory for the initial step of de-coordination of one CO ligand thus leading the active catalytic species **4**, but also to promote further step(s) in the catalytic cycle. (see SI, Figure S2) We then performed a stoichiometric reaction under argon involving **Cat 1** and 1.2 equiv. of diphenylsilane in toluene/pentane under UV light for 18 h. We then purified the active species **5** by crystallization in pentane at 5 °C, and the complex exhibited characteristic signals in <sup>1</sup>H-NMR at -8.72 ppm (Fe-H) and in <sup>29</sup>Si-NMR at +19.03 ppm (Fe-Si).<sup>[15]</sup> We then added 1 equiv. of N-benzylbenzamide, and performed the reaction during 1 h in dark. No evolution of the reaction was observed in NMR. Thus, the irradiation of the reaction mixture under UV for 1 h led to the formation of several species including several Fe-H ones, and did not permit us to differentiate if the insertion of the carbonyl moiety took place in the Fe-H or Fe-Si bond. Nevertheless, this experiment confirmed that UV-light is involved in at least the insertion step in the catalytic cycle.

Based on our previous studies and these experimental observations, we then proposed the following mechanism based on a catalytic cycle. (Scheme 4) Promoted by UV-irradiation, Fe(CO)<sub>4</sub>(IMes) **Cat 1** was able to generate a 16 e-iron(0) catalytic species **4**, which then promoted an oxidative addition of hydrosilane leading to iron hydride silyl species **5**. Via an insertion of the carbonyl moiety of the carboxamide either into the Fe-H or the Fe-Si bond of **5**, **6a** and/or **6b** can be produced and after reductive elimination, led to the active species **4** and the silylated hemiaminal intermediate **7**.<sup>[20]</sup> This hemiaminal derivative should be enough stable in the reaction mixture when using secondary silanes,<sup>[10c,18a]</sup> which should explain why no over-reduction leading to amine was observed, the corresponding aldimine being obtained only after the hydrolysis step.<sup>[21]</sup>

## Conclusions

In summary, we have described a highly efficient and controlled catalytic reduction of secondary amides using diphenylsilane as reductant promoted at room temperature under UV-light irradiation (350 nm), thanks to the use of a well-defined iron(0) catalyst, Fe(CO)<sub>4</sub>(IMes) **Cat 1**. The corresponding

aldimines were isolated in moderate to good yields. The use of an earth abundant iron catalyst, at ambient reaction conditions, under UV-light provides a practical and convenient catalytic procedure for the preparation of imines from secondary amides. This work further highlights the potential of iron catalysts in the chemoselective reduction of carboxylic derivatives. It should be underlined that this transformation was unprecedented at iron.

## Experimental Section

### Typical procedure for imine synthesis

In a dry Schlenk tube with a magnetic bar,  $\text{Fe}(\text{CO})_4(\text{IMes})$  **Cat 1** (11.8 mg, 0.025 mmol, 5 mol%), secondary amide **1** (0.5 mmol, 1 equiv.), diphenylsilane (230 mg, 1.25 mmol, 2.5 equiv.) and dry THF (0.5 mL) were added successively under an argon atmosphere. Then, the mixture was stirred upon UV-light irradiation (350 nm) at room temperature. After 16 h, the reaction was quenched by adding saturated  $\text{NaHCO}_3$  solution and stirred at room temperature overnight. Then, the mixture was extracted with dichloromethane and the organic layer was collected, dried with anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuo. The residue was distilled through using a Kugel Rohr bulb-to-bulb apparatus under vacuum, and then the pure imine product **2** was obtained through a short alumina plug (activated, basic, Brockmann I, Sigma Aldrich) eluting with petroleum ether and ethyl acetate (20:1 to 10:1).

## Supporting Information

The following supporting information is available: General experimental information, substrate preparation, optimization conditions, typical procedure for imine synthesis, Table S1, Figures S1–S2, Scheme S1, characterization data of organic compounds,  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra. The following additional references have been cited within the Supporting Information.<sup>[12,22–31]</sup>

## Acknowledgements

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## Conflict of Interests

The authors declare no conflict of interest.

## Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

**Keywords:** Aldimine · Hydrosilylation · Iron · Secondary carboxamide · UV-Light

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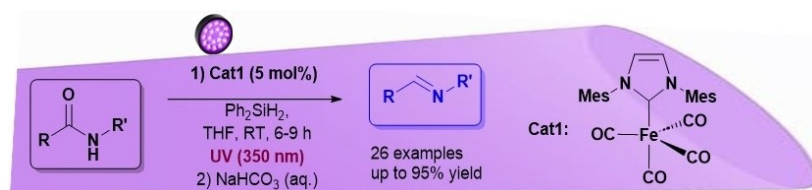
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This contribution described the first iron-catalyzed chemoselective reduction of secondary carboxamides to aldimines under hydrosilylation conditions. The reaction is catalyzed by the well defined Fe(CO)<sub>4</sub>(IMes)

complex, in the presence of 2.5 equiv. of diphenylsilane under UV irradiation (350 nm) at room temperature. [IMes = 1,3-bis (2,4,6-trimethylphenyl)-imidazol-2-ylidene]

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Iron-catalyzed Hydrosilylation of  
Secondary Carboxamides: Chemoselective  
Access to Aldimines

