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## RESEARCH ARTICLE

# Iron-catalyzed hydrosilylation of diacids in the presence of amines: a new route to cyclic amines

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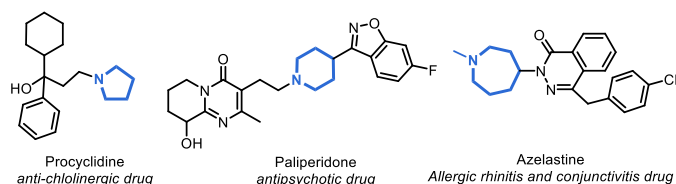
Dedicated to Prof. Pierre H. Dixneuf for his meaningful contribution to organometallic chemistry and ruthenium catalysis

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**Abstract:** Cyclic amines (such as pyrrolidines, piperidines and azepanes) are present in a large class of natural products and bioactive molecules. Herein, we present a novel chemoselective strategy for building *N*-substituted cyclic amines *via* iron catalyzed one-pot hydrosilylation starting from readily available dicarboxylic acids and amines, with hydrosilanes as the hydride sources. The described methodology allows the preparation of a wide range of *N*-alkylated and arylated cyclic amine derivatives (including pharmaceuticals Fenpiprane and Prozapine) in moderate to excellent yields, starting from inexpensive succinic, glutaric, and adipic acids with dimethyl carbonate as a green solvent.

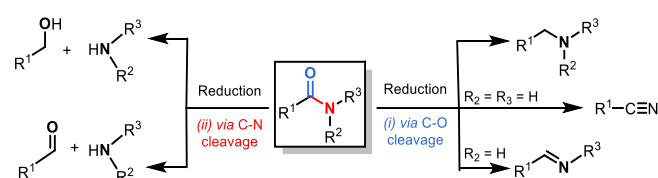
Amines are crucial derivatives in the area of molecular chemistry as demonstrated by their preponderance in pharmaceuticals, agrochemicals, dyes, and material science. Furthermore, in 2015, 170 of the top 200 drugs, representing more than US\$ 500 million retail sales contained a nitrogen atom or an amino moiety in their structure.<sup>[1]</sup> (Figure 1) Thus, the synthesis of amine compounds is still a crucial task in modern chemistry.<sup>[2]</sup>



**Figure 1.** Examples of cyclic amines as drugs.

Over the numerous methodologies developed, well exemplified catalytic reduction of carboxylic derivatives such as acids or amides is still an important area of research mainly with non-noble transition metals such as iron, manganese or cobalt. More particularly, the reduction of carboxamides is far away the most challenging to perform due to the lower electrophilicity of the carbonyl group and the chemoselectivity issues. Indeed, the reduction of amides can lead to the formation of amines, imines, enamines or nitriles by C-O bond cleavage, whereas alcohols,

aldehydes and degraded amines are obtained by cleavage of the C-N bond (Scheme 1).<sup>[3]</sup>



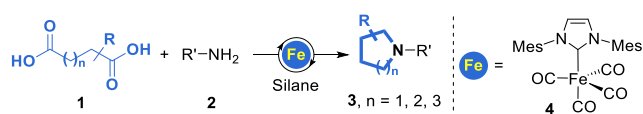
**Scheme 1.** Two pathways for the reductive transformations of amides: (i) to amines *via* dissociation of the C-O bond and (ii) to alcohols and degraded amines *via* cleavage of the C-N bond.

Additionally, catalytic hydrogenation of amides still suffered from drastic and harsh reaction conditions (elevated temperatures, high hydrogen pressures), and moderate level of chemoselectivity (deoxygenation vs hydrogenolysis pathways).<sup>[4]</sup> Since the first report on the hydrogenolysis of amides into amines and alcohols with ruthenium pincer catalysts,<sup>[5]</sup> such Ru based catalysts have shown promising activities for the selective hydrogenation of amides to amines.<sup>[6]</sup> For the other reduction pathway involving a C-O bond cleavage, a significant breakthrough was made by Cole-Hamilton<sup>[7,8]</sup> using a catalyst based on Ru(acac)<sub>3</sub> and triphos (1,1,1-tris(diphenylphosphino)methyl)ethane) in the presence of a stoichiometric amount of methanesulfonic acid able to perform the selective deoxygenation of aromatic amides leading to the corresponding amines (10-40 bar H<sub>2</sub>, 200-220 °C). The use of an additional Lewis acid such as Yb(OTf)<sub>3</sub>,<sup>[9]</sup> BF<sub>3</sub>·Et<sub>2</sub>O,<sup>[10]</sup> or B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub><sup>[11]</sup> as co-catalysts had also a beneficial effect on the activity and the chemoselectivity for the hydrogenation of secondary and tertiary amides then performed in less drastic conditions. Recently, a PNP-manganese catalyst associated to a Lewis acid was reported for the same reaction by Milstein (150 °C, 50 bar of H<sub>2</sub>).<sup>[12]</sup>

Iron can also be employed for the hydrogenation of amides.<sup>[13]</sup> Indeed, in 2016, Milstein reported the first example of a homogeneous iron-catalyzed hydrogenation of *N*-substituted 2,2,2-trifluoroacetamides using an iron-pincer (PNP) catalyst leading to the corresponding amines and trifluoroethanol through

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C-N bond cleavage (140 °C, 60 bar of H<sub>2</sub>).<sup>[14]</sup> By contrast, performing the reduction under hydrosilylation conditions<sup>[15]</sup> permitted to reverse the chemoselectivity since the C-O bond cleavage was favoured as demonstrated by the pioneering contributions of Nagashima<sup>[16]</sup> and Beller<sup>[17]</sup> using Fe<sub>3</sub>(CO)<sub>12</sub> or Fe(CO)<sub>5</sub> as pre-catalysts with either PMHS or TMS as the hydride source. Similar results could be obtained using iron-NHC complex [CpFe(CO)<sub>2</sub>(IMes)][I],<sup>[18]</sup> [bis-(*N*-Dipp-imidazole-2-ylidene)methylene-Fe(η<sup>6</sup>-benzene)],<sup>[19]</sup> and *in situ* prepared species from Fe(OAc)<sub>2</sub>, [Ph-HEMIM][OTf] and PMHS.<sup>[20]</sup> Notably, the association of two catalytic systems [NHET<sub>3</sub>][Fe<sub>3</sub>H(CO)<sub>11</sub>] and Fe(OAc)<sub>2</sub>/terpyridine efficiently reduced primary amides to primary amines.<sup>[21]</sup>



**Scheme 2.** Novel route to *N*-substituted cyclic amines via iron-catalysed hydrosilylation of diacids with amines.

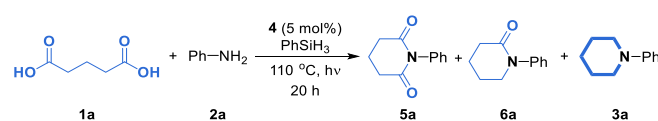
Following our recent development on cyclic amine synthesis via iron-catalyzed one-pot sequential transformations under hydrosilylation conditions starting from keto-acids or ω-amino fatty acid derivatives,<sup>[22]</sup> we herein report the use of diacids as the starting substrates to prepare pyrrolidines, piperidines and azepanes. (Scheme 2) Indeed, over the other alternative methods involving such iron-catalyzed reductive amination sequences, diols can be also envisaged as starting materials. In this area, significant breakthrough has been made in the development of methods for the cyclization of primary amines starting from diols via hydrogen borrowing catalyzed with noble metals,<sup>[23]</sup> base metals,<sup>[24]</sup> γ-Al<sub>2</sub>O<sub>3</sub><sup>[25]</sup> as well as organic catalysts.<sup>[26]</sup> The advantages of such methodologies were clearly atom-economic and without generation of harmful waste (only water as by-product) even if most of these systems required high reaction temperature. Additionally, Barta reported elegant methodologies based on hydrogen borrowing pathways involving iron-catalyzed alkylation of amines with alcohols<sup>[27]</sup> or decarboxylative *N*-alkylation of cyclic α-amino acids.<sup>[28]</sup>

On the other hand, carboxylic acids can be interesting alternative starting materials for *N*-alkylation of amines. Indeed, a straightforward catalytic *N*-alkylation of amines with carboxylic acids was reported by Beller *et al.* in 2014 using Karstedt's type catalyst and hydrosilanes as reducing reagents.<sup>[29]</sup> Even if diacids are more readily available, to the best of our knowledge, the direct hydrosilylation of diacids with amines yielding *N*-substituted cyclic amines remains unknown to date. Nevertheless, it must be noticed that the reduction of diesters with anilines under hydrogenation conditions led to *N*-aromatic heterocycles when catalyzed by Ru(acac)<sub>3</sub> associated with triphos.<sup>[30]</sup> However harsh reaction conditions (220 °C) were generally required and its scope was limited to aniline derivatives.

Based on our previous contributions, we then began our initial optimization work using the iron(0) *N*-heterocyclic carbene complex Fe(CO)<sub>4</sub>(IMes) **4** as the catalyst (5 mol%) for the reaction of glutaric acid **1a** with aniline **2a** in the presence of PhSiH<sub>3</sub> (6 equiv.). Under solvent free conditions, after 20 h at 100 °C upon visible light activation (24 W compact fluorescent

lamp), both conversion (70%) and selectivity were moderate as a mixture of *N*-phenylpiperidine **3a**, *N*-phenylglutarimide **5a** and *N*-phenyl-2-piperidone **6a** was obtained in a ratio of 54/11/5 (Table 1, entry 1). Performing the reaction in toluene under similar conditions didn't permit to increase the conversion, but the selectivity towards the formation of desired product **3a** increased to 67% yield, along with 3% of **6a**. Conducting the transformation at 110 °C for 20 h permitted to convert 75% of the starting materials and obtained **3a** exclusively (75%, Table 1, entry 3).

**Table 1.** Catalyzed hydrosilylation of glutaric acid with aniline.<sup>[a]</sup>



Entry	PhSiH <sub>3</sub> [equiv.]	Solvent	Additive [mol%]	Conv. [%] <sup>[a]</sup>	Yield [%] <sup>[a]</sup>		
					5a	6a	3a
1 <sup>[b]</sup>	6	Neat	-	70	11	5	54
2 <sup>[b]</sup>	6	Toluene	-	70	0	3	67
3	6	Toluene	-	75	0	0	75
4	6	Me-THF	-	70	0	0	70
5	6	Dioxane	-	70	0	0	70
6	6	DMC	-	72	0	0	72
7 <sup>[c]</sup>	6	Toluene	-	69	69	0	0
8	4	Toluene	-	40	12	4	24
9	2	Toluene	-	38	25	5	8
10 <sup>[d]</sup>	6	DMC	-	50	50	0	0
11 <sup>[d]</sup>	-	DMC	-	0	0	0	0
12	-	DMC	-	0	0	0	0
13	6	DMC	FeCl <sub>3</sub> (10)	32	32	0	0
14	6	DMC	Fe(OTf) <sub>3</sub> (10)	26	26	0	0
15	6	DMC	FeCl <sub>2</sub> (10)	71	0	0	71
16	6	DMC	Fe(OTf) <sub>2</sub> (10)	83	0	0	83
17	6	DMC	Fe(OTf) <sub>2</sub> (20)	90	0	0	90
18	6	DMC	Fe(OTf) <sub>2</sub> (30)	84	17	0	67

[a] General conditions: **4** (5 mol%), **1a** (0.5 mmol), **2a** (0.5 mmol), PhSiH<sub>3</sub> (0-6 equiv.) and solvent (1 mL), visible light irradiation, 110 °C, 20 h; then hydrolysis (THF/NaOH 2 N). The conversions and yields were determined by <sup>1</sup>H NMR using dibromomethane as the internal standard. [b] 100 °C. [c] [CpFe(CO)<sub>2</sub>(IMes)][I] **7** (5 mol%) as the catalyst. [d] in the absence of Fe catalyst **4**.

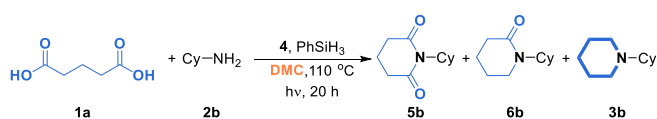
Substituting toluene by 2-Me-THF, 1,4-dioxane or dimethylcarbonate (DMC) did not increased the conversion, even if **3a** was still exclusively obtained (70-72%; Table 1, entries 4-6). Nevertheless, since DMC gave comparable efficiency, its greener character prompted us to select it for the scope of this transformation.<sup>[31]</sup> Interestingly, using an iron(II) complex such as [CpFe(CO)<sub>2</sub>(IMes)][I] **7** (5 mol%) under similar conditions in toluene at 110 °C, 69% of glutaric acid **1a** was converted, but the chemoselectivity was switched as only the *N*-phenylglutarimide **5a** was obtained, showing that this iron(II) catalyst was able to promote only the transamidation reaction, but not the reduction of **5a** leading to **6a** then **3a** (Table 1, entry 7). Additionally, reducing the amount of phenylsilane to 4 equiv. decreased the efficiency of the reaction as only 40% of conversion was observed and a mixture of **3a**, **5a** and **6a** was obtained in a ratio of 24/12/4. With 2 equiv. of PhSiH<sub>3</sub>, similar conversion (38%) of **1a** was observed, but with **5a** (25%) as the major product (Table 1, entries 8-9).

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Noticeably, with 6 equiv. of phenylsilane, the reaction reached 50% conversion in the absence of catalyst **4** leading to exclusively *N*-phenylglutarimide **5a** (Table 1, entry 10), whereas in the absence of both silane and Fe catalyst, or using 5 mol% of **4** without silane, no reaction occurred. (Table 1, entries 11-12). These results seem to indicate that the excess of PhSiH<sub>3</sub> promotes the formation of imide **5a** (see also SI Scheme S1), via the intermediate of silylated diester obtained from diacid derivatives. Taking into account that even if the conversion were not complete when using **4** as catalyst, *N*-phenylpiperidine **3a** was obtained solely, indicating that the reduction of **5a** and **6a** was faster than the formation of **5a** via transamidation between **1a** and **2a**, making the latter the rate-limiting step.

Lewis acids are known to promote the (trans)amidation of carboxylic acid derivatives with anilines.<sup>[32]</sup> Thus, several Lewis acids were evaluated in this reaction in association with the Fe(0) catalyst **4**. Using iron(III) based Lewis acids such as FeCl<sub>3</sub> or Fe(OTf)<sub>3</sub> (10 mol%) led to disappointing results as only partial conversions into imide **5a** were observed (32 and 26%, respectively, Table 1, entries 13-14). Among the trials with different Lewis acids (SI Table S1), Fe(OTf)<sub>2</sub> exhibited the most promising results: using Fe(OTf)<sub>2</sub> (10 mol%) with phenylsilane (6 equiv.) increased the conversion to 83% and *N*-phenylpiperidine **3a** was exclusively obtained (Table 1, entry 16). Increasing the Fe(OTf)<sub>2</sub> amount to 20 mol% enhanced the yield of **3a** to 90%, while the use of 30 mol% of Fe(OTf)<sub>2</sub> has a detrimental effect on both the reactivity and selectivity (84% conversion, **5a**:**3a** = 17:67, Table 1, entries 17-18). Thus, the optimized conditions to obtain *N*-arylpiperidine were 5 mol% of **4** in combination with 20 mol% of Fe(OTf)<sub>2</sub> and 6 equiv. of phenylsilane in DMC at 110 °C for 20 h. It is worth mentioning that attempts with different hydrosilanes such as Ph<sub>2</sub>SiH<sub>2</sub>, Et<sub>3</sub>SiH, Me<sub>2</sub>PhSiH, PMHS (polymethylhydrosiloxane), TMDS (1,1,3,3-tetramethyldisiloxane) gave no conversion of aniline.

**Table 2.** Hydrosilylation of glutaric acid with cyclohexylamine.<sup>[a]</sup>



Entry	<b>4</b> [mol%]	PhSiH <sub>3</sub> [equiv.]	T [°C]	Conv. [%]	Yield [%]		
					<b>5b</b>	<b>6b</b>	<b>3b</b>
1	5	6	110	99	0	0	99
2	5	4	110	99	0	0	99
3	5	2	110	99	0	40	60
4	2.5	4	110	95	0	0	95
5	-	6	110	99	99	0	0

[a] General conditions: **4** (0-5 mol%), **1a** (0.5 mmol), **2a** (0.5 mmol), PhSiH<sub>3</sub> (2-6 equiv.) and DMC (1 mL), visible light irradiation, 110 °C, 20 h; then hydrolysis (THF/NaOH 2 N). The conversions and yields were determined by <sup>1</sup>H NMR using dibromomethane as the internal standard.

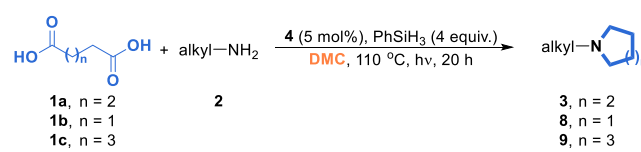
We then focussed on the reaction of alkylamine (cyclohexylamine **2b**) with glutaric acid **1a** in order to synthesize *N*-alkylpiperidines (Table 2). The optimization study was firstly performed using **4** as the catalyst (5 mol%) in the presence of PhSiH<sub>3</sub> (6 equiv.) in DMC. After 20 h at 110 °C, *N*-cyclohexylpiperidine **3b** was generated in quantitative NMR-yield (Table 2, entry 1), notably without the production of other intermediates: *N*-cyclohexylglutarimide **5b** and *N*-cyclohexyl-2-

piperidone **6b**, and without the use of Lewis acid. The amount of PhSiH<sub>3</sub> can be decreased to 4 equiv. without any loss of activity and selectivity, as **3b** was still obtained quantitatively. (Table 2, entry 2) However, the selectivity dropped when decreasing the amount of PhSiH<sub>3</sub> to 2 equiv. or the catalyst loading to 2.5 mol% (Table 2, entries 3-4). Finally, in the absence of the catalyst **4**, **5b** was found to be the sole product, demonstrating that Fe catalyst **4** was crucial to produce **3b**.

With the optimized conditions for the catalyzed hydrosilylation of diacids in the presence of arylamines and alkylamines (Table 1, entry 17, and Table 2, entry 2, respectively) in hand, the substrate scope and its limitation were next studied (Table 3 for alkylamines, Table 4 for arylamines).

Starting from glutaric acid **1a**, various alkylamines such as cyclohexylamine, 1-hexylamine and benzylamine can be applied leading to the corresponding piperidines in excellent isolated yields (**3b-d**, 93-95%, Table 3). The substitution of the benzyl moiety with electron donating or withdrawing groups such as methoxy or trifluoromethyl had nearly no influence on the efficiency of the transformation, leading to **3e** and **3f** in 91% and 85% yields, respectively. Additionally, heteroaromatic moiety, for instance, furyl and benzimidazolyl groups can be tolerated as **3g** and **3h** were generated in 91% and 80% yields, respectively. Noticeably, increasing the steric hindrance of the amine partner decreased the efficiency of the reaction: indeed, using 2,4,6-trimethylbenzylamine or  $\alpha$ -methylbenzylamine led to the corresponding piperidines **3i** and **3j** in moderate yields, 73% and 68%, respectively.

**Table 3.** Hydrosilylation of diacids in the presence of aliphatic primary amines.<sup>[a]</sup>



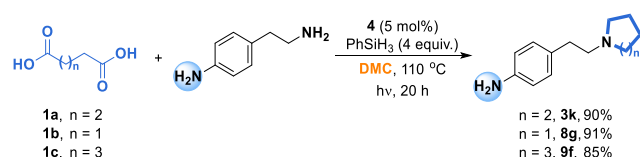
Product	Yield [%]
<b>3b</b> , n = 2	94%
<b>3c</b> , n = 2	93%
<b>3d</b> , n = 1	95%
<b>3e</b> , n = 1	91%
<b>3f</b> , n = 3	85% <sup>[b]</sup>
<b>3g</b> , n = 2	91%
<b>3h</b> , n = 2	80% <sup>[b]</sup>
<b>3i</b> , n = 2	73%
<b>3j</b> , n = 2	68%
<b>8a</b> , n = 2	78%
<b>8b</b> , n = 2	87%
<b>8c</b> , n = 2	89%
<b>8d</b> , n = 2	90%
<b>8e</b> , n = 2	96%
<b>8f</b> , n = 2	91% <sup>[b][c]</sup>
<b>9a</b> , n = 2	77%
<b>9b</b> , n = 2	68%
<b>9c</b> , n = 2	34% <sup>[b]</sup>
<b>9d</b> , n = 2	75%
<b>9e</b> , n = 2	70%

[a] General conditions: **4** (5 mol%), diacid **1** (0.5 mmol), amine **2** (0.5 mmol), PhSiH<sub>3</sub> (4 equiv.) and DMC (1 mL), visible light irradiation, 110 °C, 20 h; then hydrolysis (THF/NaOH 2 N). Isolated yields of the products are shown. [b] NMR yield. [c] succinic acid **1b** (1.0 mmol, 2 equiv. to amine **2**), PhSiH<sub>3</sub> (8 equiv.), 48 h.

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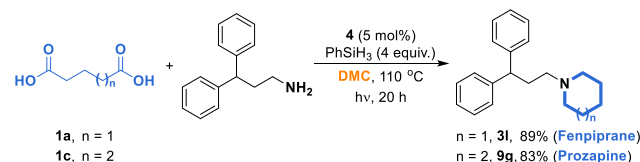
Starting from succinic acid **1b**, pyrrolidines **8** can be also efficiently prepared in one step. Thus, **8a** and **8b** can be synthesized from the corresponding amines, 2,4-dimethoxybenzylamine and furfurylamine, in 78% and 87% yields, respectively. Remarkably, using an amino-alcohol such as 6-aminohexanol, a chemoselective transformation occurred as the pyrrolidine **8c** bearing a pending hydroxyl group was prepared in 89% yield. Furthermore, using more steric hindered 1-adamentylamine, **8d** was obtained in 90% yield. As expected, cyclohexanemethylamine was a suitable substrate leading to **8e** in 96% yield. Interestingly, ethylene-diamine also reacted selectively with succinic acid giving the corresponding bis-piperidine **8f** in 91% yield.

Larger cyclic amines, such as azepanes, can be also produced in moderate to good yields using this methodology: starting from adipic acid **1c**, azepanes **9a** and **9b** were obtained in 77% and 68% yields when reacted with *p*-methoxybenzylamine and 2,4,6-trimethylbenzylamine (Table 3). With the more steric hindered 1-(1-naphyl)ethylamine, **9c** was detected in a lower yield (34%), showing that the steric hindrance had a drastic effect on the activity for the azepane formation. The reaction also tolerated heteroaromatic groups such as thienyl- and pyridyl-methylamine which led to **9d** and **9e** with 75% and 70% yields, respectively. Nevertheless, it should be noticed that unsaturated amines such as allylamine and propargylamine led to unsatisfactory selectivity, as the C=C and C≡C were partially reduced.



**Scheme 3.** *N*-Alkylation of alkylamines bearing aniline moiety.

Since it was potentially competitive to alkylate anilines and aliphatic amines with diacids, we decided to perform the reaction with 4-(2-aminoethyl)aniline as the substrate associated with succinic, glutaric, and adipic acids. (Scheme 3) Noticeably, the *N*-alkylation of aliphatic amine moiety occurred exclusively as the corresponding cyclic amines **3k**, **8g** and **9f** were isolated in 85%-91% yields, leaving aniline group untouched.



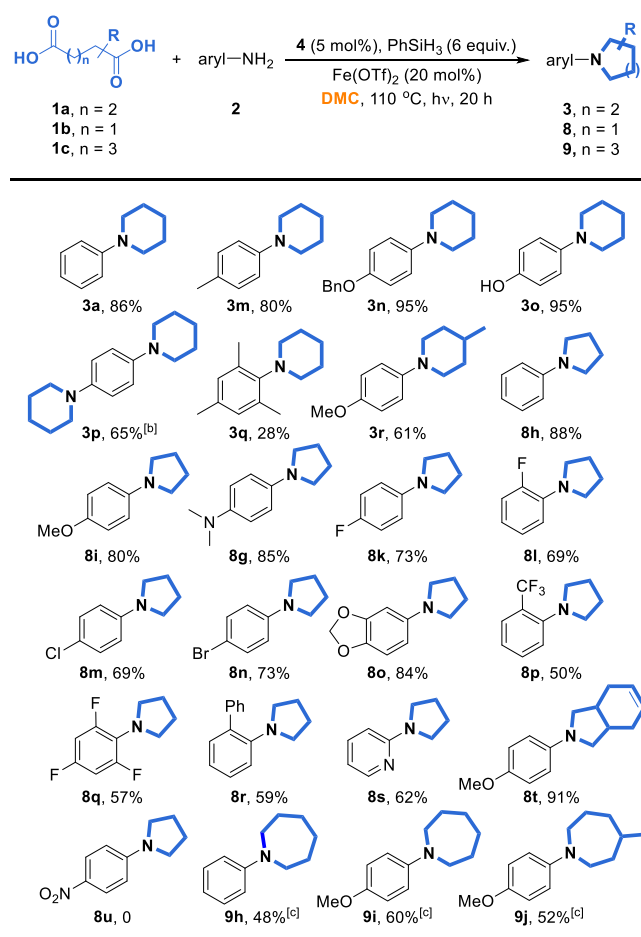
**Scheme 4.** One-pot catalytic synthesis of Fenpiprane **3l** and Prozapine **9g**.

Furthermore, we have demonstrated the synthetic utility of this methodology in the preparation of drug molecules Fenpiprane **3l** and Prozapine **9g**, which are used to treat functional gastrointestinal disorders, and as antispasmodic drug, respectively<sup>[33]</sup> (Scheme 4). Thus, reaction of the 3,3-

diphenylpropylamine and glutaric acid **1a** (adipic acid **1c**) afforded **3l** and **9g**, in 89% and 83% isolated yields.

In order to prepare *N*-aryl cyclic amines (Table 4), the optimized reaction conditions depicted in Table 1, entry 17 was employed. By reaction of glutaric acid **1a** with aniline, *p*-toluidine and 4-(benzyloxy)aniline, the corresponding *N*-arylpiperidines **3a**, **3m** and **3n** were obtained in 80%-95% yields. Good functional group tolerance was achieved starting from *p*-aminophenol, as **3o** was isolated in 95% yield. The transformation can be also conducted with *p*-phenylenediamine yielded the bis-pyrrolidine **3p** in 65%. By contrast, the use of 2,4,6-trimethylaniline didn't permit to obtain efficiently the corresponding piperidine **3q** (28%), indicating that steric hindrance decreased drastically the reactivity. Substituted glutaric acid, like 3-methylglutaric acid **1a'** was also a suitable coupling partner with *p*-anisidine, leading to **3r** in 61% yield.

**Table 4.** Hydrosilylation of diacids in the presence of primary arylamines.<sup>[a]</sup>



[a] General conditions: **4** (5 mol%), **1** (0.5 mmol), Fe(OTf)<sub>2</sub> (20 mol%), amine **2** (0.5 mmol), PhSiH<sub>3</sub> (6 equiv.) and DMC (1 mL), visible light irradiation, 110 °C, 20 h; then hydrolysis (THF/NaOH 2 N). Isolated yields of the products are shown. [b] glutaric acid **1a** (1.0 mmol, 2 equiv.), PhSiH<sub>3</sub> (12 equiv.), 48 h. [c] Fe(OTf)<sub>2</sub> (50 mol%).

The reaction of succinic acid **1b** with aniline, *p*-methoxy, *p*-dimethylamino, *p*-fluoro, *o*-fluoro, *p*-chloro and *p*-bromoanilines led to pyrrolidines **8h-n** in 69-88% yields, highlighting the functional group tolerance towards electron donating and halogeno groups. However, deiodinated pyrrolidine product was



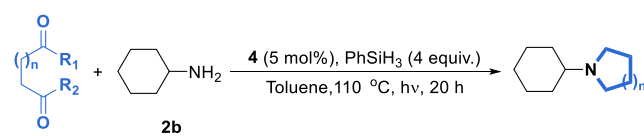
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mainly obtained starting from 4-iodoaniline. Notably, an important building block for pharmaceuticals such as 3,4-(methylenedioxy)aniline was effectively transformed to piperidine **8o** in 84% yield. Electron deficient anilines like *o*-trifluoromethyl and 2,4,6-trifluoroaniline were transformed into pyrrolidines **8p** and **8q** in moderate yields (50% and 57%, respectively). Additionally, *o*-phenylaniline led to **8r** in 59% yield highlighted the drastic effect of the steric hindrance. Heteroaromatic amine like 2-aminopyridine was also successfully applied leading to **8s** in 62% yield. Diacid bearing alkenyl moiety such as *cis*-4-cyclohexene-1,2-dicarboxylic acid **1b'** gave **8t** in 91% yield, with the remote C=C untouched. However, diacid with conjugated C=C, such as maleic acid and itaconic acid, led to a mixture of products due to the easy reduction of the C=C bond. Noticeably, anilines bearing more electron-withdrawing nitro, cyano substituents was not converted into the corresponding product.

Additionally, when adipic acid **1c** was used in association with aniline under standard conditions, the desired product *N*-phenylazepane **9h** was detected in ca. 10% NMR-yield. Noticeably, diol resulting of the reduction of diacid was observed in GC-MS as a by-product. To overcome the low reactivity of adipic acid with arylamine, 50 mol% of Fe(OTf)<sub>2</sub> was employed to obtain **9h** and **9i** in 48% and 60% yields, respectively, starting from aniline and *p*-anisidine. 3-Methyladipic acid can also provide **9j** in 52% yield. Albeit this protocol was quite general for aliphatic diacids, the attempts to perform the reaction of phthalic acid with either alkylamines or arylamines gave a mixture of products including the expected isoindoline products.

Even though the organometallic catalytic process involving the Fe complex **4** in catalyzed hydrosilylation reactions has been studied,<sup>[34]</sup> highlighting the crucial role of the light activation to generate a 16 electron active species able to promote the oxidative addition of the hydrosilane thus generating the related H-Fe-SiR<sub>3</sub> intermediate which was isolated and characterized, we were interested to gain some insights of the reaction pathways. Then various dicarboxylic acid derivatives were employed as substrates to produce cyclic amines starting from cyclohexylamine **2b** (Table 5).

**Table 5.** Hydrosilylation of various diacid derivatives with cyclohexylamine. <sup>[a]</sup>

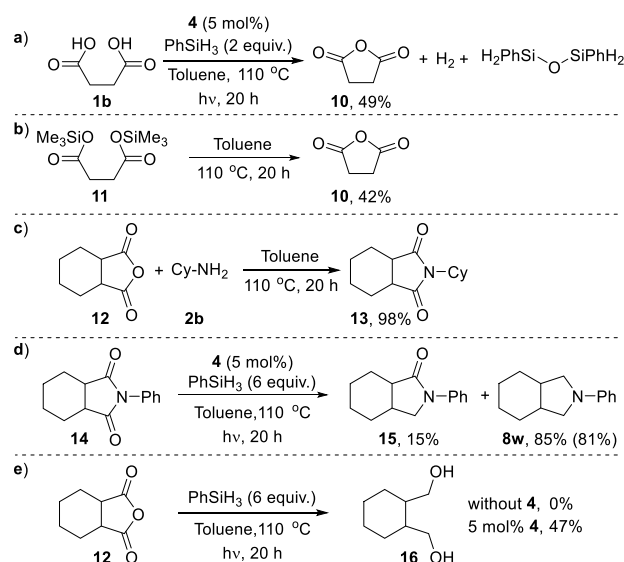


Entry	R <sub>1</sub>	R <sub>2</sub>	n	Conv. <sup>[a]</sup>	Yield <sup>[a]</sup>
1	OMe	OMe	2	16	14
2	OMe	OMe	3	6	4
3	NH <sub>2</sub>	OMe	3	n.d.	n.d.
4	R <sub>1</sub> , R <sub>2</sub> = -NH (imide)		1	n.d.	n.d.
5 <sup>[b]</sup>	R <sub>1</sub> , R <sub>2</sub> = -O- (anhydride)		1	>99	>99 (93)

[a] General conditions: **4** (5 mol%), diacid derivative (0.5 mmol), cyclohexylamine (0.5 mmol), PhSiH<sub>3</sub> (4 equiv.) and toluene (1 mL). visible light irradiation, 110 °C, 20 h; then hydrolysis (THF/NaOH 2 N). Conversions and yields were detected by <sup>1</sup>H NMR using dibromomethane as the internal standard. Isolated yields are shown in parentheses. [b] using *cis*-1,2-cyclohexanedicarboxylic anhydride as substrate.

Under the optimized reaction conditions (Table 2, entry 2), dimethyl glutarate and adipate gave the corresponding cyclic amines in 14% and 4% NMR yields, respectively (Table 5, entries 1-2), while methyl adipamate and succinimide were totally inactive (entries 3-4). These results seem to imply that such derivatives were probably not involved as intermediates. Unexpectedly, *cis*-1,2-cyclohexanedicarboxylic anhydride led to the corresponding cyclic amine **8v** in 93% isolated yield (entry 5), showing that cyclic anhydride may be a plausible intermediate of the reaction.

Further control experiments were then performed and summarized in Scheme 5. In the absence of amine, succinic acid **1b** was converted into succinic anhydride **10** in 49% NMR yield, in the presence of both Fe catalyst **4** (5 mol%) and PhSiH<sub>3</sub> (2 equiv.) (Scheme 5a and SI Table S2). Importantly, molecular hydrogen was detected by *in situ* <sup>1</sup>H-NMR at 4.47 ppm (Figure S1), and siloxane PhH<sub>2</sub>Si-O-SiPhH<sub>2</sub> was also identified by GC-MS. It is described that silyl esters can be generated from dehydrogenative coupling of carboxylic acids and silanes under the catalysis of either transition metals or organo-catalysts.<sup>[35]</sup>



**Scheme 5.** Control experiments. Conversion and yield were detected by <sup>1</sup>H NMR using dibromomethane as the internal standard, isolated yield in parentheses.

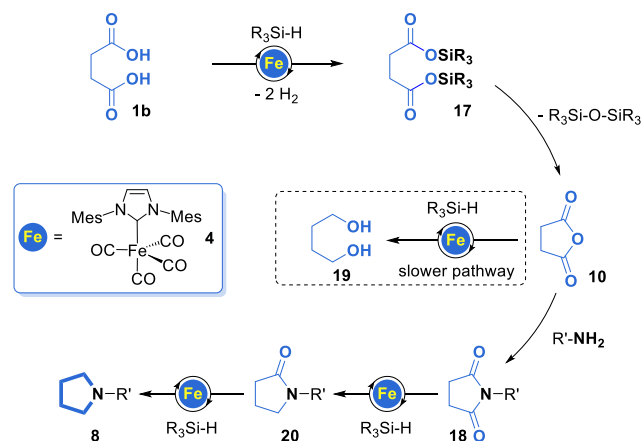
Thus, we heated bis(trimethylsilyl)succinate **11** at 110 °C for 20 h, and as expected, succinic anhydride **10** was produced in 42% yield (Scheme 5b), which indicated that cyclic anhydride can be produced *via* the intermediacy of silylated diester obtained from diacid and silane. Even if it was reported that imides can be prepared by condensation of dicarboxylic anhydrides and primary amines, we set up such reaction starting from *cis*-1,2-cyclohexanedicarboxylic anhydride **12** and cyclohexylamine **2b**. Indeed, the corresponding imide **13** was prepared quantitatively (Scheme 5c).

Afterwards, the direct hydrosilylation of imide was performed with hexahydro-*N*-phenylphthalimide **14** as the substrate, under reaction conditions described in Table 1, entry 3. Hexahydro-2-phenyl-isoindoline **8w** was thus isolated in 81% yield. Noticeably, 15% of amide **15** was also produced as a by-product.

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(Scheme 5d, and SI Table S3) Such results demonstrated that the production of cyclic amines from imide went through the reduction of amide *via* a Fe-catalyzed sequence. Additionally, since diol was formed during the formation of *N*-arylazapane (Table 4), it was shown that diol **16** was obtained in 47% yield by direct hydrosilylation of cyclic anhydride **12** under the same reaction conditions (Scheme 5e). In order to rule out a radical process, the addition of TEMPO (1 equiv.) to the reaction was performed. A full conversion of amine starting material was achieved giving 56% desired products and 41% amide by-product along with 3% of imide (SI Scheme S2), indicating that a radical process may not happen during the catalytic process.

Finally, according to the above control experiments, a proposed reaction pathway is depicted in Scheme 6. The sequence started with the reaction of the diacid **1** such as succinic acid **1b** with hydrosilanes leading to the silylated diester **17** *via* a dehydrogenative silylation and liberation of H<sub>2</sub>. After releasing of R<sub>3</sub>Si-O-SiR<sub>3</sub>, the cyclic anhydride intermediate **10** was formed, and reacted with amines to generate the imide **18**, step where the presence of the Fe catalyst **4** was not necessary. Alternatively, cyclic anhydride **10** could also be reduced into diol **19** with silanes under the catalysis of Fe complex **4**, however it was slower compared with the formation of imide **18**. Afterwards, the first reduction of imide **18** into amide **20** took place *via* iron catalysed hydrosilylation. Then amide **20** was further reduced to the final cyclic amine product **8** under the same conditions.<sup>[22]</sup> On the other hand, compared with alkylamines, arylamines were less reactive to produce *N*-arylated cyclic amines, as Lewis acid was required to promote the transamidation step. (Scheme 5c and SI Table S4).



**Scheme 6.** Proposed possible reaction pathway.

In summary, we have developed for the first time the Fe-catalyzed hydrosilylation of diacids in the presence of amines to access *N*-substituted cyclic amines. This method has several advantages: i) it utilizes environmentally benign non-noble transition metal iron based complex as catalyst, ii) it enables one-pot synthesis of cyclic amines, iii) it starts from inexpensive dicarboxylic acids and amines, iv) it exhibits good functional group tolerance, v) it allows the production of drug molecules Fenpiprane and Prozapine in good yields, and vi) it proceeds in dimethyl carbonate as a green solvent. Further detailed control

experiments have shown that the cyclic anhydrides formed *in situ* from diacids played a key intermediate ahead of imides.

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**Keywords:** iron catalysis • hydrosilylation • dicarboxylic acid • cyclic amines • one-pot

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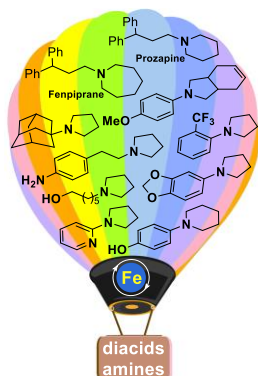
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## Entry for the Table of Contents



**A ride in an "iron" balloon:** a novel strategy for building *N*-substituted cyclic amines is reported via iron catalyzed one-pot hydrosilylation of dicarboxylic acids with amines, using silanes as hydride source. 50 examples of amine derivatives, including drug molecules Fenpiprane and Prozapine, were prepared in good yields with dimethyl carbonate as a green solvent.