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Pushing Back the Limits of Hydrosilylation: Unprecedented Catalytic Reduction of Organic Ureas to Formamidines

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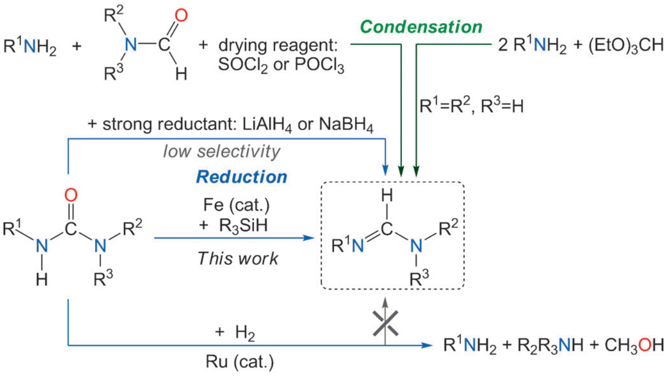
Catalytic hydrosilylation of carbonyl functional groups is gaining an increasing interest in synthetic organic chemistry because it circumvents important limitations of the more classical hydrogenation or metal-hydride mediated reduction methodologies.[1] Indeed, hydrosilanes are practical reducing agents because they have a mild reduction potential and are less sensitive to moisture than $LiAlH_4$, DIBAL, or $NaBH_4$. Moreover, the slightly polar and weaker Si–H bond (bond dissociation energy (BDE) 92 $kcal\,mol^{-1}$ in SiH_4)[2] is easier to activate than the strong non-polar H–H bond (BDE 104 $kcal\,mol^{-1}$)[3] and hydrosilylation reactions can be promoted using noble metal-free catalysts or organocatalysts under mild reaction conditions, without the need for high-pressure apparatus.[1,4] As a result, catalytic hydrosilylation can achieve highly chemo- and regio-selective transformations and recent examples include the reduction of carboxylic acids,[4f,5] esters[4e,6] (to ethers and aldehydes) and amides.[4e,6f,7] Nonetheless, the methodology still has limitations and, so far, the catalytic hydrosilylation of organic ureas to formamidines remains unknown. Indeed, the C=O group in urea derivatives is the least electrophilic function within the series of carbonyl groups in aldehydes, ketones, esters, amides, carbonates, carbamates, and ureas.[8,9] This effect primarily results from strong resonance effects between the vacant $\pi^*_{C=O}$ orbital and the vicinal nitrogen lone pairs in urea. As a result, strong reductants such as alumino- and boro-hydrides have been utilized so far for the reduction of urea derivatives to formamidines.[10] They, however, also lead to over-reduction to the aminal derivative, because the formamidine product is more easily reduced than the urea starting material.[10] In 2011, Milstein and coworkers were the first to successfully promote the hydrogenation of organic ureas, utilizing tailor-made ruthenium catalysts.[8] However, the ruthenium catalysts promote C–N over C–O bond cleavage and the resulting formamide intermediate is hydrogenated faster than the urea starting material, leading to the formation of methanol and free amines (Scheme 1).[8]

Substituted formamidines are important chemicals in the industry for their biological activities and pharmacological properties (bactericidal, fungicidal and insecticidal).[11] Moreover, they are common building blocks in organic chemistry and utilized as reagents for the synthesis of drugs, ligands and N-heterocycles or as protecting groups for primary amines.[12,13] The reduction of substituted ureas is an attractive route to formamidines because symmetric and unsymmetric organic ureas are easily accessible and stable compounds. They can also be prepared using CO_2 as a carbon(IV) source.[14] In principle, the catalytic reduction of ureas with hydrosilanes would offer an attractive alternative to current condensation strategies that require strong and/or toxic drying agents, such as phosphorus oxychloride, trifluoroacetic anhydride, or thionyl chloride,[15] as promoters (Scheme 1). Yet, to the best of our knowledge, such transformations remain undiscovered. Here we report the first examples of catalytic hydrosilylation of urea derivatives (Scheme 1). The reduction takes place under mild conditions and the iron catalyst selectively promotes reduction to the formamidine products with no over-reduction to the aminal derivatives.



Scheme 1. Synthetic routes for the preparation of formamidines.

Among organic ureas, *N*,*N*′-diphenyl-urea (**1a**) was selected as a benchmark substrate for the novel hydrosilylation reaction, because the aromatic substituents are expected to increase the reduction potential of the N–C(O)–N carbonyl function. Motivated by the urge to develop noble metal-free catalysts, important efforts have been recently devoted to explore the potential of iron catalysts in reduction processes, with compelling success.[5a,6d,7a,d,i–j,16] Noticeably, Beller and coworkers have shown that iron hydride complexes supported by phosphine ligands are able to promote the hydrogenation of the kinetically stable CO_2 molecule to formate derivatives.[16a] Encouraged by these advances, the catalytic activity of a variety of iron salts was tested in the hydrosilylation of *N*,*N*′-diphenyl-

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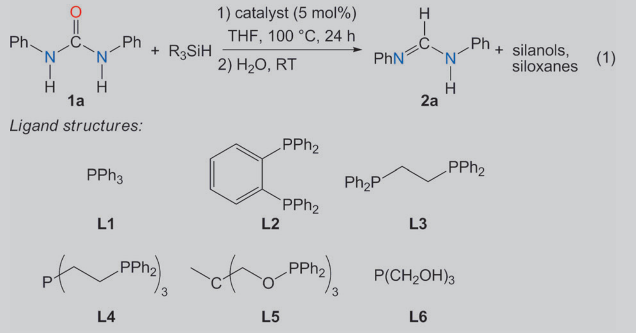
Table 1. Catalytic hydrosilylation of *N*,*N*′-diphenyl urea (**1a**) to formamidine **2a**, as depicted in Equation (1).



Entry	Catalyst[a]	Ligand [mol %]	Silane (R_3SiH) [eq]	Yield[b] [%]
1	–	–	$PhSiH_3$ (1.0)	<1
2	$FeCl_2$	–	$PhSiH_3$ (1.0)	<1
3	$FeCl_3$	–	$PhSiH_3$ (1.0)	<1
4	$FeSO_4{\cdot}7H_2O$	–	$PhSiH_3$ (1.0)	<1
5	$Fe(acac)_3$	–	$PhSiH_3$ (1.0)	<1
6	$Fe(acac)_2$	–	$PhSiH_3$ (1.0)	5
7	$Fe(BF_4)_2{\cdot}6H_2O$	–	$PhSiH_3$ (1.0)	46
8	$Fe(acac)_2$	**L1** (20)	$PhSiH_3$ (1.0)	15
9	$Fe(acac)_2$	**L2** (10)	$PhSiH_3$ (1.0)	34
10	$Fe(acac)_2$	**L3** (10)	$PhSiH_3$ (1.0)	15
11	$Fe(acac)_2$	**L4** (5)	$PhSiH_3$ (1.0)	98
12	$Fe(acac)_2$	**L5** (5)	$PhSiH_3$ (1.0)	27
13	$Fe(acac)_2$	**L6** (20)	$PhSiH_3$ (1.0)	20
14	$Fe(BF_4)_2{\cdot}6H_2O$	**L1** (20)	$PhSiH_3$ (1.0)	38
15	$Fe(BF_4)_2{\cdot}6H_2O$	**L2** (10)	$PhSiH_3$ (1.0)	65
16	$Fe(BF_4)_2{\cdot}6H_2O$	**L3** (10)	$PhSiH_3$ (1.0)	42
17	$Fe(BF_4)_2{\cdot}6H_2O$	**L4** (5)	$PhSiH_3$ (1.0)	81
18	$Fe(BF_4)_2{\cdot}6H_2O$	**L5** (5)	$PhSiH_3$ (1.0)	43
19	$Fe(BF_4)_2{\cdot}6H_2O$	**L6** (20)	$PhSiH_3$ (1.0)	15
20	$Fe(acac)_2$	**L4** (5)	Ph_2SiH_2 (1.5)	<1
21	$Fe(acac)_2$	**L4** (5)	PMHS (3.0)	<1
22	$Fe(acac)_2$	**L4** (5)	Et_3SiH (3.0)	<1
23	$Fe(acac)_2$	**L4** (5)	$(EtO)_3SiH$ (3.0)	11

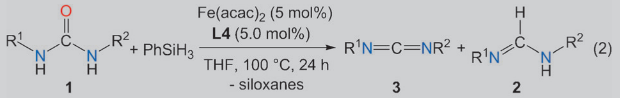
[a] All catalysts were employed at 5 mol %. [b] Determined by GC/MS (using biphenyl as an internal standard) and ^1H NMR analyses of the crude mixture.

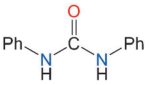
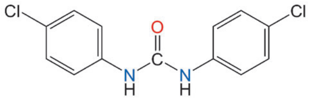
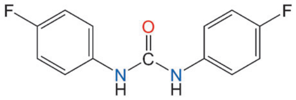
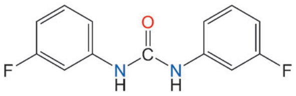
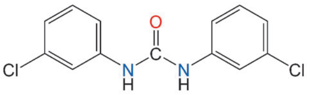
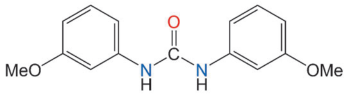
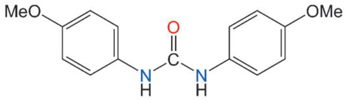
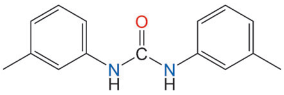
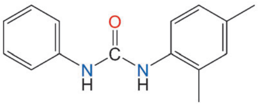
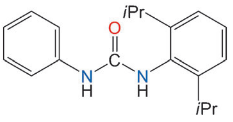
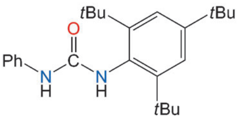
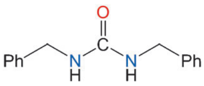
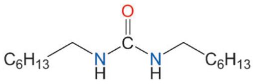
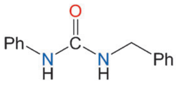
urea (**1a**). In the presence of a catalytic amount of $FeCl_2$, $FeCl_3$, $Fe(SO_4){\cdot}7H_2O$ or $Fe(acac)_3$ (5 mol %), addition of 1 equiv $PhSiH_3$ to a THF solution of **1a** led to no reaction and the starting materials were recovered unreacted after 24 h at 100 °C (Entries 2–5, Table 1). Nonetheless, iron(II) complexes $Fe(acac)_2$ and $Fe(BF_4)_2{\cdot}6H_2O$ exhibit a modest, but promising, catalytic activity, promoting reduction of **1a** to its formamidine derivative **2a** in 5 and 46 % yields, respectively, under identical reaction conditions (Entries 6 and 7, Table 1). These preliminary results establish the feasibility of the catalytic reaction depicted in Equation (1) (Table 1).

Supporting phosphine ligands were then screened, so as to increase the catalytic activity of both $Fe(acac)_2$ and $Fe(BF_4)_2{\cdot}6H_2O$ (Entries 8–19, Table 1). Overall, the addition of phosphines proved highly beneficial and substantially enhanced the reactivity and/or stability of the catalyst. Noticeably, the tetra-phosphine **L4** ligand, originally developed by King and coll.,[17] leads to the most efficient catalytic systems and **1a** is reduced to formamidine **2a** with an excellent 98 % yield, using an equimolar mixture of $Fe(acac)_2$ and **L4** (5 mol %) with 1 equiv $PhSiH_3$, after 24 h at 100 °C (Entry 11, Table 1). A somewhat lower 81 % yield is observed when $Fe(BF_4)_2{\cdot}6H_2O$ is used in place of $Fe(acac)_2$ (Entry 17, Table 1). A change of the hydrosilane indicates that $PhSiH_3$ is the most reactive reductant in the hydrosilylation of **1a**, among the reactants tested. Although $(EtO)_3SiH$ affords **2a** in 11 % yield using $Fe(acac)_2$ and **L4** (5 mol %), Ph_2SiH_2, polymethylhydrosiloxane (PMHS) and Et_3SiH are completely inactive in the reduction of **1a** (Entries 20–23, Table 1). This trend in reactivity tends to support a mechanism involving the formation of an iron-hydride intermediate in the catalytic hydrosilylation of ureas.[18] THF is the most profitable solvent for the reaction in Equation (1). In the less polar Et_2O solvent, **2a** is formed in 57 % yield (with 5 mol % ($Fe(acac)_2$ + **L4**)), however this yield does not exceed 17 % in toluene, pyridine, 1,4-dioxane, or acetonitrile. Notably, DMF and DMSO are found to be unsuitable for the hydrosilylation of ureas, because the solvent molecules are themselves reactive towards reduction. Similarly, the more benign alcohols (2-propanol or *tert*-butanol)[19] are readily dehydrogenated in the presence of $PhSiH_3$ and the iron catalyst. Likely, in the near future, the development of catalysts able to utilize the less basic PMHS hydrosilane will circumvent this limitation.

Having in hand an efficient catalytic system for the hydrosilylation of **1a**, the scope of reactive substituted ureas was explored, utilizing $Fe(acac)_2$ and **L4** (5 mol %) as a catalytic system, with $PhSiH_3$ as a reductant (Table 2). All the substrates tested (**1a**–**1o**) were found reactive under the applied conditions with conversions ranging from 69 to 98 %, with the exception of the very bulky urea **1k**, which is converted to other products in a modest 49 % yield. Noticeably, the nature of the substituents on the nitrogen atoms has a major influence on the outcome of the reaction and the yields of formamidines **2** vary from 29 to 98 % depending on the substitution scheme (13 % for **2k**). Introducing electron-withdrawing groups (Cl and F) on the aryl rings of *N*,*N*′-diphenylurea (**1a**) has little impact on the reactivity of the urea and formamidines **2b**–**2e** are obtained in good 56-81 % yields (Entries 2–5, Table 2). On the other hand, electron-donating groups somewhat deactivate the production of formamidines **2** (Entries 6-8, Table 2). For example, in the presence of a methyl group in the *meta*-position of the aryl rings, formamidine **2h** is obtained in 29 % yield (Entry 8, Table 2). Importantly, carbodiimide **3h** is formed in 69 % yield in this transformation, accounting for the excellent 98 % conversion yield for **1h**. Indeed, carbodiimides **3** were successfully detected in the hydrosilylation of **1**, in various proportions depending on the electronic nature of N-groups (5–69 % yields). This reactivity suggests that carbodiimides **3** are reaction intermediates in the hydrosilylation of **1** to **2** (see below). Interestingly, unsymmetric *N*,*N*′-diarylureas **1i** and **1j** are reduced to the corresponding unsymmetric formamidines **2i** and **2j** in good 74 and 63 % yields, respectively (Entries 9 and 10, Table 2). As expected, *N*,*N*′-dialkylureas are more difficult to reduce and lead to the accumulation of the carbodiimide intermediate. Nonetheless, formamidines **2l** and **2m** can be obtained in 39 and 64 % yields, respectively, using 10 mol %

Table 2. Catalytic hydrosilylation of organic ureas **1** to formamidines **2**, as depicted in Equation (2).

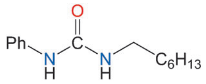


Entry	Substrate (**1**)	Conv.[a] [%]	Yield of **3**[a] [%]	Yield of **2**[a] [%]
1	 **1a**	98	< 1	98[b]
2	 **1b**	86	5	81
3	 **1c**	69	13	56
4	 **1d**	84	24	58
5	 **1e**	90	30	60
6	 **1f**	94	47	47
7	 **1g**	86	55	31
8	 **1h**	98	69	29
9	 **1i**	87	10	74
10	 **1j**	83	20	63
11	 **1k**	49	36	13
12	 **1l**	98[c]	59[c]	39[c]
13	 **1m**	95[c]	31[c]	64[c]
14	 **1n**	92	16	76

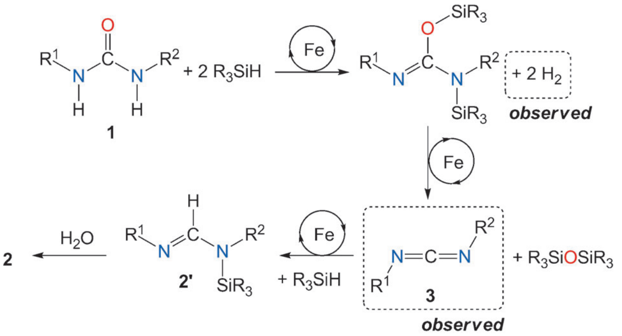
$Fe(acac)_2$ + **L4** and 2 equiv $PhSiH_3$. Additionally, the mixed aryl-alkyl *N*-substituted ureas **1n** and **1o** have a greater electrophilicity and are hydrosilylated to **2n** and **2o** in good yields (>65%, Entries 14 and 15, Table 2). Importantly, in all these examples (Entries 1–15, Table 2), no over-reduction of the urea **1** to the aminal derivative was observed. Whereas the reduction of ureas with metal-hydrides (e.g. $LiAlH_4$ or $NaBH_4$) has a low selectivity and leads to a mixture of aminal and formamidine products,[10] this reactivity clearly highlights the benefit of catalytic hydrosilylation.

Though the results gathered in Table 2 demonstrate, for the first time, the feasible reduction of ureas using hydrosilanes, this new method for the synthesis of formamidines suffers from a modest selectivity, for some of the substrates. As such, mechanistic insights on the nature of the reactive intermediates would be informative for the future design of more active catalysts. From a mechanistic perspective, the product distributions obtained in Table 2 suggest the involvement of carbodiimide species **3** as reactive intermediates in the hydrosilylation of organic ureas **1** to formamidines **2**. Though ureas **1** are stable in the presence of hydrosilanes (Entry 1, Table 1), they are dehydrated to the corresponding carbodiimides **3** in the presence of the iron catalyst (Table 2). This transformation is reminiscent of the dehydration of primary amides to nitriles using hydrosilanes[7d] and likely proceeds through dehydrogenative silylation of both N–H bonds of the di-substituted urea and subsequent elimination of the siloxane by-product. Catalytic silylation of N–H bonds in amines is indeed well documented[20] and H_2 evolution was successfully detected by monitoring the hydrosilylation of **1a** by using ^1H NMR spectroscopy, in the presence of $Fe(acac)_2$ + **L4** (5 mol%) and 1 equiv $PhSiH_3$. Hydrosilylation of carbodiimides to *N*-silylformamidines is a relatively unexplored transformation. Only two catalysts were found active for this reaction, namely $PdCl_2$ and $[(PPh_3)_3RhCl]$, and they function at elevated temperature (150 °C).[21] Importantly, we found that the phosphine iron catalysts are able to promote the hydrosilylation of carbodiimides to formamidines in high yields. As depicted in Equation (3), $Fe(BF_4)_2{\cdot}6H_2O$ + **L4** efficiently promotes the hydrosilylation of both aliphatic (**3p** and **3q**) and aromatic (**3r**) carbodiimides, whereas $Fe(acac)_2$ + **L4** is mostly able to reduced *N*,*N*′-di-*p*-tolylcarbodiimide (**3r**) to **2r** in 60% yield. Overall, these findings support the mechanistic proposal presented in Scheme 2. It relies on the iron-catalyzed dehydration of urea **1** to carbodiimide **3** promoted by two equivalents of the hydrosilane reagent. Subsequent catalytic hydrosilylation of **3** affords the *N*-silylformamidine derivative **2**′ which is readily hydrolyzed to **2**.

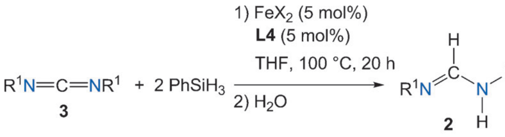
Table 2. (Continued)

Entry	Substrate (1)	Conv.[a] [%]	Yield of **3**[a] [%]	Yield of **2**[a] [%]
15	 **1 o**	88	23	65

[a] Determined by GC/MS (using biphenyl as an internal standard) and ^1H NMR analyses of the crude mixture. [b] Average isolated yield for **2 a**, over three experiments: 90 %. [c] Results obtained using Fe(acac)$_2$ (10 mol %) and **L4** (10 mol %), in the presence of 2.0 equiv PhSiH$_3$.



Scheme 2. Proposed mechanistic scheme for the iron-catalyzed hydrosilylation of ureas **1** to formamidines **2**.

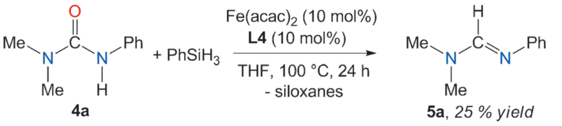


(3)

Yields (%):

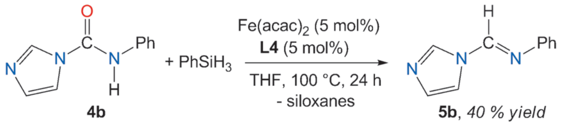
FeX_2:	Fe(acac)$_2$	Fe(BF$_4$)$_2$·6H$_2$O
2p, R^1 = *i*Pr	10	99
2q, R^1 = Cy	14	99
2r, R^1 = *p*-tolyl	60	76

The involvement of carbodiimides as reaction intermediates in the reduction of ureas **1** may limit the scope of reactive substrates to *N*,*N*′-di-substituted-ureas and we, therefore, explored the reactivity of tri-substituted ureas **4** in the new iron-catalyzed hydrosilylation reaction [Eq. (4) and (5)]. Interestingly, *N*,*N*-dimethyl-*N*′-phenylurea **4 a** is reduced to **5 a** in 25 % yield using 10 mol % of Fe(acac)$_2$ + **L4** and 1 equiv PhSiH$_3$. Though modest, this conversion indicates that hydrosilylation of ureas to formamidines may proceed through different yet convergent pathways and that the direct hydrosilylation of the N-CO-N carbonyl function is also feasible without prior activation by dehydration. Replacing the electron donating methyl groups in **4 a** with an imidazole ring facilitates the hydrosilylation and **4 b** is reduced to **5 b** in 40 % yield, without reduction of the imidazole ring, using 5 mol % Fe(acac)$_2$ + **L4**.



(4)

In conclusion, we have developed the first catalytic hydrosilylation reaction of organic ureas. Iron catalysts, consisting of a mixture of an iron(II) salt (Fe(acac)$_2$ or Fe(BF$_4$)$_2$·6 H$_2$O) with a commercially available tetra-phosphine ligand, are able to promote the formation of symmetric and unsymmetric formamidines without over-reduction to the aminal derivatives. This protocol has been successfully applied to 17 different ureas with different electronic and geometric properties. The main catalytic pathway was shown to involve the dehydration of the urea reagent to its corresponding carbodiimide derivative which is subsequently reduced by the hydrosilane. Future efforts will be devoted to increasing the catalytic activity and selectivity of the iron system to utilize inexpensive hydrosilanes, such as PMHS and TMDS, in this transformation.



(5)

Experimental Section

Detailed descriptions of experimental and spectroscopic results are given in the Supporting Information.

Acknowledgements

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Keywords: hydrosilylation · iron · reduction · silanes · ureas

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