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Calcium-catalysed synthesis of amines through imine hydrosilylation: an experimental and theoretical study†

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A method to reduce aldimines through hydrosilylation is reported. The catalytic system involves calcium triflimide ($\text{Ca}(\text{NTf}_2)_2$) and potassium hexafluorophosphate (KPF_6) which have been shown to act in a synergistic manner. The expected amines are obtained in fair to very high yields (40–99%) under mild conditions (room temperature in most cases). To illustrate the potential of this method, a bioactive molecule with antifungal properties was prepared on the gram scale and in high yield in environmentally friendly 2-methyltetrahydrofuran. Moreover, it is shown in this example that the imine can be prepared *in situ* from the aldehyde and the amine without isolating the imine. The mechanism involved has been explored experimentally and through DFT calculations, and the results are in accordance with an electrophilic activation of the silane by the calcium catalyst.

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Introduction

Amines constitute highly important building blocks in organic synthesis due to their omnipresence in natural products, polymers,¹ pharmaceuticals² and agrochemicals.^{3,4} Among the synthetic strategies towards these key compounds, catalytic reduction of imines including hydrogenation, hydrogen transfer or hydrosilylation appear to be efficient methodologies. In the last few years, hydrosilylation processes involving silanes as the H source significantly contributed to the preparation of amines.^{5,6} Hydrosilanes, readily produced on the industrial scale, indeed constitute useful reducing agents due to their air- and water stability, ease of handling and ability to be activated under mild conditions. They thus appear as attractive alternatives to molecular hydrogen often requiring high temperature and pressure conditions as well as a specific set-up. Although ytterbium-, aluminium-, boron^{7,8}- and even ionic liquid⁹-based or organic¹⁰ catalysts have been shown to promote imine hydrosilylation, the most ubiquitous catalysts for these transformations involve transition metals. Historically, the first systems reported involved noble ones (ruthenium, rhodium, iridium, and palladium) and later on, some catalysts based on more Earth abundant metals such as copper,¹¹ zinc,¹² nickel,¹³ and iron^{14–17} have been developed.⁵

Some of the complexes required multi-step ligand synthesis and/or are air- or moisture sensitive. Our objective is to provide the actual toolbox for imine hydrosilylation with a catalytic system involving a benign metal, with attractive features for organic chemists, namely ready availability and ease of handling (air- and moisture stable). We then turned our attention to calcium. Generally, alkaline earth metals (Ae = Mg, Ca, Sr, and Ba) attracted much attention over the last decade and catalytic systems have been reported to promote a wide range of processes including ring-opening polymerization,¹⁸ C–C or C–heteroatom bond-forming transformation,^{19,20} dehydrocoupling^{21–24} or hydroelementation of C=C, C=O or C=N bonds.^{25–28} Along these lines, alkaline earth complexes were shown to promote hydrosilylation of olefins^{29–31} or pyridines.^{32–35} Interestingly, with regard to non-activated C=N bonds, Sarazin *et al.* reported stoichiometric hydrosilylation of imine ligands in barium complexes.³⁶ In addition, a recent breakthrough by Harder *et al.* demonstrated for the first time the ability of calcium, strontium and barium complexes involving amide and/or benzyl ligands to catalyse the hydrosilylation of aldimines and one ketimine with phenylsilane.^{37,38}

In this report, a commercial and moisture stable calcium salt $\text{Ca}(\text{NTf}_2)_2$ is shown to act in a synergistic manner with KPF_6 and in the absence of any additional ligands to catalyse the hydrosilylation of aldimines under mild conditions. DFT studies have been carried out to get insight into the involved mechanism. To the best of our knowledge, while calcium-based Lewis acids have emerged as important catalysts in

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green chemistry, $\text{Ca}(\text{NTf}_2)_2$ has not been used yet to promote imine hydrosilylation.^{20,28} In addition, it is the first time that calcium triflimide is shown to activate Si–H bonds, opening new prospects in the field of hydrosilylation reactions as well.

Results and discussion

Imine **1a**, which results from the condensation of 4-bromobenzaldehyde and 4-iodoaniline, was chosen as the model substrate. The performance of several commercial calcium salts in the hydrosilylation of **1** with phenylsilane at room temperature was evaluated. Although calcium hydroxide and alkoxides were inefficient (no conversion of **1a**), $\text{Ca}(\text{NTf}_2)_2$, a calcium precursor that has a strongly electron-withdrawing and weakly coordinating counter anion, allowed the formation of the expected amine **2a**, however, with low yield (10%) (Table 1, entry 1). The addition of catalytic amounts of KPF_6 (20 mol%) enabled a significant increase in the performance (entry 2), with **2a** being quantitatively obtained. It is noteworthy that $\text{Ca}(\text{NTf}_2)_2$ and KPF_6 acted in a synergistic manner, with KPF_6 being inefficient when used alone (entry 3). It has previously been shown that $\text{Ca}(\text{NTf}_2)_2$ and PF_6^- salts undergo anion metathesis to form KNTf_2 and $\text{Ca}(\text{NTf}_2)\text{PF}_6$.²⁰ The latter salt, which is more Lewis acidic than $\text{Ca}(\text{NTf}_2)_2$ and has two binding sites available on the calcium center, was reported to activate a wide range of substrates such as cyclopropanes,^{39,40} carbonyl compounds,^{41,42} alcohols,^{43–48} alkenes^{49,50} and more recently sulfonyl^{51,52} fluorides.^{20,28,53} $\text{Ca}(\text{NTf}_2)\text{PF}_6$, whose Lewis acidity has been evaluated by the Childs method,⁴¹ has also been associated with hexafluoroisopropanol as the solvent and the resulting system has been shown by Gandon and Lebœuf to be highly active in various transformations including aza-Piancatelli,^{54,55} hydroarylation,⁵⁶ hydroamidation⁵⁷ and hydroacyloxylation⁵⁸ reactions. It is noteworthy that under our con-

ditions, KNTf_2 alone was unable to promote imine **1a** hydrosilylation (entry 4), suggesting that $\text{Ca}(\text{NTf}_2)\text{PF}_6$ is the catalytically active species. Furthermore, triflimic acid was unable to promote hydrosilylation, which ruled out the possibility that traces of Tf_2NH were the source of the observed activity and confirmed that the calcium center played a role in the catalytic process.

The amounts of catalyst and additive could be successfully decreased to 10 mol% without significant change (entry 5). Under these conditions, by decreasing the amount of silane by two equivalents (2 equiv. instead of 4, entry 6), amine **2a** could be obtained quantitatively when the reaction was stopped after 16 hours at 25 °C (entry 6). It is worth noting that **2a** is formed in 86% yield after only 6 hours, suggesting that the conversion is attained before 16 h. Decreasing the amount of $\text{Ca}(\text{NTf}_2)\text{PF}_6/\text{KPF}_6$ (1 : 1) from 10 to 5 mol% only led to a slight decrease in the yield of amine **2a** from 99 to 87% (entry 7).

With these optimized conditions in hand, phenylsilane was replaced with several cheaper counterparts including diphenylsilane, triphenylsilane, dimethylphenylsilane, triethylsilane and 1,1,3,3-tetramethyldisiloxane. However, none of the tested silanes led to the conversion of imine **1a** at 25 °C.

Next, the scope of the method was investigated on aromatic aldimines using $\text{Ca}(\text{NTf}_2)_2/\text{PF}_6^-$ (1 : 1) (10 mol%) as the catalytic system (Fig. 1).

(Benzylidene)phenylamine **1b** was quantitatively transformed into amine **2b**. Imines **1c** and **1d**, both derived from toluidine, underwent hydrosilylation in good yields as well (98 and 82% isolated yields for **2c** and **2d**, respectively), even in the case of the bulkier *ortho*-substituted naphthyl derivative **1d**. Substrates **1e–g** bearing electron-donating methoxy substituents were converted in fair to high yields (66, 82 and 99% for **2f**, **2g** and **2e**, respectively). While imine **1e** was fully converted within 16 h at 25 °C, **2f** and **2g** derived from electron-rich *p*-methoxyaniline were less reactive and an increase in temperature to reflux THF (65 °C) was required to improve the conversions. The hydrosilylation of imines **1h–j** bearing electron-withdrawing trifluoromethyl groups was then investigated. Amines **2h**, **2i** and **2j** could be formed quantitatively and isolated in very high yields (88, 97 and 90%, respectively). Here again, the effect of the substituent was dependent on its position: while **1h** and **1j** produced from electron-poor *p*-trifluoromethylaniline were fully converted at 25 °C within 6 and 16 h, respectively, imine **1d** bearing the CF_3 substituent on the “aldehyde” side required higher temperature to be reduced (refluxing THF instead of 25 °C). As in the case of **1a**, the halogenated imines **1k** and **1l** were quantitatively transformed into the corresponding amines **2k** and **2l** under the standard conditions. The method was shown to be compatible with several functional groups including esters (90% and 82% isolated yields for **2m** and **2n**), cyano substituents (88% and 76% isolated yields for **2o** and **2p**) and ketones (94% yield for **2q**). Significantly lower yields were obtained for amines **2r–u** bearing alkyl substituents at N in refluxing THF. Increasing the amount of the calcium catalyst from 10 to 20 mol% did not significantly improve the performance. Therefore, this

Table 1 Optimisation study for the reduction of imine **1a** with calcium pre-catalysts

Entry	[Ca] (mol%)	Additive (mol%)	Eq. PhSiH_3	Yield 2a ^{a,b}	Reaction conditions	
					[Ca] (x mol%)	additive (y mol%)
1	$\text{Ca}(\text{NTf}_2)_2$ (20)	—	4	10	—	—
2	$\text{Ca}(\text{NTf}_2)_2$ (20)	KPF_6 (20)	4	99	—	—
3	—	KPF_6 (20)	4	0	—	—
4	—	KNTf_2 (20)	4	0	—	—
5	$\text{Ca}(\text{NTf}_2)_2$ (10)	KPF_6 (10)	4	99	—	—
6	$\text{Ca}(\text{NTf}_2)_2$ (10)	KPF_6 (10)	2	99 (86 ^c)	—	—
7	$\text{Ca}(\text{NTf}_2)_2$ (5)	KPF_6 (5)	2	87	—	—

^a Typical procedure: $\text{Ca}(\text{NTf}_2)_2$, KPF_6 , PhSiH_3 and THF (1 mL) were stirred at 25 °C for 10 minutes before adding aldimine **1a** (0.25 mmol) and THF (0.5 mL). The reaction mixture was stirred at 25 °C for 16 h and next hydrolysed with MeOH (1.5 mL) and NaOH (2 M, 1.5 mL).

^b Yield determined by NMR using 1,3,5-trimethoxybenzene as the standard (selectivity >99%). ^c After 6 h instead of 16.



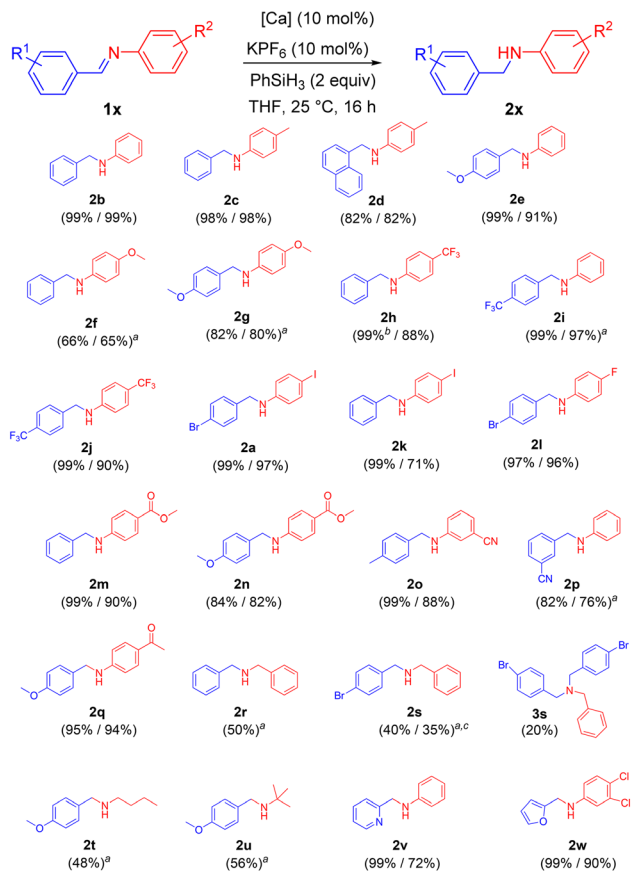


Fig. 1 Scope of the catalytic system (NMR yield/isolated yield). Typical procedure (NMR yields): Ca(NTf₂)₂ (0.025 mmol), KPF₆ (0.025 mmol), PhSiH₃ (0.5 mmol), and THF (1 mL) were stirred at 25 °C for 10 minutes before adding aldimine **1x** (0.25 mmol) and THF (0.5 mL). The reaction mixture was stirred at 25 °C for 16 h and then hydrolysed with MeOH (1.5 mL) and NaOH (2 M, 1.5 mL). Yield was determined by NMR using 1,3,5-trimethoxybenzene as the standard. Typical procedure (isolated yields): Ca(NTf₂)₂ (0.1 mmol), KPF₆ (0.1 mmol), PhSiH₃ (2 mmol), and THF (4 mL) were stirred at 25 °C for 10 minutes before adding aldimine **1x** (1 mmol) and THF (2 mL). The reaction mixture was stirred at 25 °C for 16 h and then hydrolysed with MeOH (6 mL) and NaOH (2 M, 6 mL). ^a 65 °C. ^b Quantitative NMR yield after 6 h. ^c Formation of *N,N*-di(4-bromobenzyl)benzylamine **3s** (20% isolated yield, see the ESI†).

system appears to be complementary to the one reported by Harder, which has been shown to be particularly efficient for imines bearing an alkyl group at N and aryl substituents at C.³⁷ Interestingly, in addition to the expected amines **2r** and **2s**, tertiary amines were also formed; for example, *N,N*-di(4-bromobenzyl)benzylamine **3s**, isolated in 20% yield (see ESI p. S12†), is an appealing starting compound for application in pharmaceuticals or sensors.⁵⁹ The synthetic pathway to explain the formation of this by-product is still unclear. The heteroaromatic imines **1v** and **1w** were quantitatively reduced and the expected amines were isolated in good to very high yields (72 and 90% for **2v** and **2w**, respectively). While **2v** is a ligand with potential for application in catalysis, **2w** has potential for application in medicinal chemistry due to its antifungal properties and also as a precursor of antitubercular agents.^{60,61}

At this stage, we were keen to get insights into the processes involved in the previously described hydrosilylation.

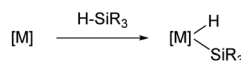
From a mechanistic point of view, two main hydrosilane activation pathways have been previously proposed (Scheme 1): (i) the Chalk–Harrod and the modified Chalk–Harrod mechanism occurring for *e.g.* with rhodium or platinum catalysts and relying on two-electron oxidative addition and reductive elimination steps (Scheme 1A); and (ii) an ionic mechanism in which a Lewis acidic catalyst enhances the electrophilic character of the silicon center through the activation of the Si–H bond (Scheme 1B).

In Ae-catalyzed C=C or C=N hydrosilylation, metal hydride species play a key role in the mechanism and are proposed to be the active species.^{29–32,37,62} In some of these reactions, the pre-catalyst involves the metal–hydrogen bond. The calcium hydrido complexes can also be generated from amide/alkyl/benzyl calcium precursors and silanes through σ -bond metathesis (Scheme 1C). This process has been widely described and exploited in catalytic reactions including hydrogenation or hydro-elementation,⁶² and more recently in the redistribution of hydrosilanes⁶³ or dehydrogenative silylation of aromatic ethers.⁶⁴

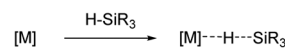
Under our conditions, calcium hydroxide, alkoxides and even calcium triflimidate Ca(NTf₂)₂ alone are not efficient to promote the hydrosilylation of imine **1a**. The fact that hydrosilylation only occurs in the presence of the highly Lewis acidic calcium salt Ca(NTf₂)PF₆ might suggest that the mechanism involves an electrophilic activation of the Si–H bond (Scheme 1B). Such a pathway was reported for the hydrosilylation of ketones and imines promoted by perfluoroarylboranes such as B(C₆F₅)₃ (Scheme 1B).^{65–69} In these processes, hydrosilylation proceeded more rapidly in the case of least basic substrates.⁶⁷ Under our conditions, the electronic properties of the substituents were shown to have an effect on the catalytic performance. For example, electron-poor imine **1h** with a CF₃ group at the *para* position of the imine nitrogen was significantly more reactive than imine **1f** with an electron-donating methoxy group at the same position. Indeed, while **1h** was quantitatively converted into **2h** within 6 h at room temperature (Fig. 1, note d), **1f** required heating to reach a conversion of 66% after 16 h.

Next the interaction between the Ca(NTf₂)PF₆ catalyst and each of the substrates, imines and silane, was investigated. As

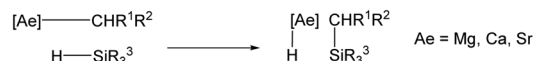
A- Chalk-Harrod and modified Chalk-Harrod mechanisms



B- Lewis acid mechanisms (electrophilic Si-H activation)



C- Mechanisms involving σ -bond metathesis: case of Ae-alkyl/amide complexes

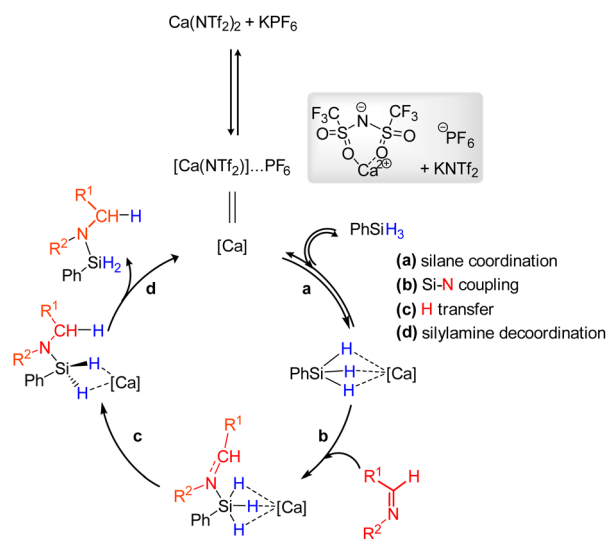


Scheme 1 Main mechanisms of silane activation pathways.



a first attempt, the evolution of a stoichiometric mixture of the calcium catalyst and imine **1h** in deuterated THF was then monitored by ^1H NMR at different temperatures (25 °C to -65 °C and back to 25 °C). No obvious change could be observed in the imine spectrum irrespective of the temperature, suggesting that the presence of the hydrosilane is required for the two substrates to react together. The same behaviour was observed in the case of more electron-rich imine **1f**. The same NMR experiment was then performed in the case of phenylsilane. The addition of one equivalent of Ca(NTf₂)PF₆ to phenylsilane did not induce any change in the ^1H NMR spectrum of the silane at room temperature. Next ^1H NMR spectra were collected at lower temperatures, from 25 °C to -65 °C. Interestingly at -25 °C (ESI § 4.1†), the appearance of broad signals at around 6–6.4 ppm was observed and the signals became increasingly sharp when the temperature was decreased to -65 °C (ESI, Fig. S1 p. S14†). The phenomenon was shown to be reversible when the temperature returned to room temperature (ESI, Fig. S2 p. S14†). These observations suggest a weak coordination of the silane to calcium.^{67,70}

From all these experimental observations, we propose a putative catalytic cycle (Scheme 2). The process starts with the generation of the catalytically active species and highly Lewis acidic Ca(NTf₂)PF₆ (represented as [Ca]), where the PF₆⁻ counter-anion is not expected to be in the first coordination sphere.^{20,71} The first step of the catalytic cycle would consist in the coordination of the silane to the calcium center Ca(NTf₂)⁺ (Scheme 2, step a). The subsequent intermolecular nucleophilic attack of the imine on the silicon center may lead to the silyliminium intermediate (Scheme 2, step b), by analogy with the mechanism proposed in the case of B(C₆F₅)₃.⁶⁹ In the following step c, H-transfer may occur. The last decoordination step d would enable the release of the expected silylamine and the regeneration of the catalytically active calcium species.



Scheme 2 Mechanism of the Ca-catalyzed hydrosilylation of imines proposed by analogy with that of B(C₆F₅)₃.

To gain a better understanding of the mechanism of this catalytic hydrosilylation, DFT studies were carried out with a dispersion corrected hybrid functional and an implicit model for the solvent (THF). Natural bond orbital (NBO) analyses of the stationary points of the potential energy surface have been carried out. Full computational details are given in the ESI.†

The Ca²⁺ complex with the NTf⁻ ligand, and the substrates (**2b** imine and PhSiH₃) were represented in full. The PF₆⁻ counter-anion was supposed to be non-coordinated and was not taken into account for the modelling.

The overall reaction is found to be exergonic ($\Delta_r G^\circ = -16.9$ kcal mol⁻¹) and requires a Gibbs activation energy of 26.1 kcal mol⁻¹ relative to that of the separate reagents (Fig. 2). The driving force of the reaction relies on the C–H and Si–N bonds, which are slightly stronger than the broken Si–H and C=N bonds. The reaction mechanism is found to be the succession of two elementary steps.

The reaction sequence begins with the coordination of the imine and PhSiH₃ to the metal cation, leading to adduct **A**. The first step requires a low activation barrier ($\Delta G^\ddagger = 21.3$ kcal mol⁻¹, relative to that of adduct **A**, *i.e.* 14.0 kcal mol⁻¹ relative to the energy reference), and corresponds to the step during which the Si–N bond is formed, leading to intermediate **B** ($d_{\text{Si-N}} = 2.181$ Å and 2.019 Å for **TSAB** and **B**, respectively). It is noteworthy that for this intermediate **B**, the Si atom is found to be pentavalent and at the center of a trigonal bipyramid. The NBO analysis for this intermediate shows that its relative stability is essentially based on favorable donor–acceptor interactions, on the one hand between the N lone-pair and the three $\sigma^*_{\text{Si-H}}$ antibonds (mainly with the $\sigma^*_{\text{Si-H}}$ trans to N) and on the other hand between the three $\sigma_{\text{Si-H}}$ bonds and the vacant 3s orbital of Ca (see ESI § 5.3†). It is also important to note that all attempts to optimize the structure of such a reaction intermediate, where Si is hypervalent, in the absence of

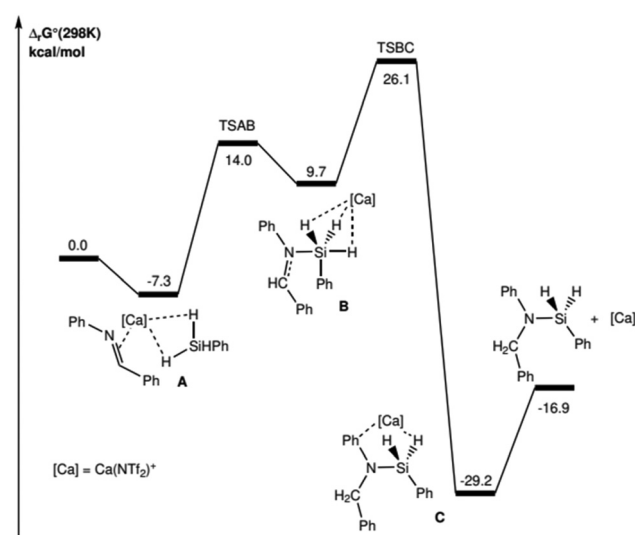


Fig. 2 Gibbs energy profile (kcal mol⁻¹) for the hydrosilylation of **2b** imine catalysed by Ca(NTf)⁺.



the $\text{Ca}(\text{NTf}_2)^+$ catalyst, have been unsuccessful: the stability of this intermediate is a key aspect of the process and can only be ensured with the electrophilic assistance of Ca. The intermediate **B** also has a characteristic ^1H NMR signature: calculations suggest an isotropic chemical shift δ for the H in alpha from the C functional of the imine to 9.0 ppm and shifts for the 3 H bonded to the Si and in interaction with Ca, between 5.0 and 5.8 ppm (ESI § 5.4†); these calculated values are consistent with the transiently experimentally observed values of the chemical shift (see ESI Fig. S3 p. S15†).

The second step corresponds to the transition from the intermediate **B** to the product **C** and is the kinetic determining step ($\Delta G^\ddagger = 26.1 \text{ kcal mol}^{-1}$ with respect to the reference energy). This step corresponds to the β -migration of one of the three H atoms carried by the Si towards the imine C atom. An NBO analysis of the electronic structure of this TSBC transition state shows clearly that the transferred H has a strong hydride character (the corresponding NBO charge is $-0.81e$). This electrophilic nature allows for better understanding of the greater efficiency of the process for imines substituted with an electron-withdrawing group with respect to imines substituted with electron-donating groups (**2h** vs. **2f**, Fig. 2), which enables, respectively, the stabilisation/destabilisation of this transition state (see ESI § 5.3†).

The final step corresponds to the decoordination of the silylamine to the metal (adduct **C**), leading to the free $\text{Ca}(\text{NTf}_2)^+$ complex and the reaction product without interactions.

The proposed mechanism, consistent with the experimental observations previously presented, favors an electrophilic Si–H activation pathway.

Lastly, to illustrate the potential of the method for application in organic chemistry, the catalytic system reported here was applied to the synthesis of bioactive amine **2w** on the gram-scale through reductive amination and by optimizing the conditions (solvent and amounts of metal and silane, Scheme 3). Therefore, in this synthesis, equimolar amounts of 2-furfural, a chemical obtained from biomass,⁷² and 3,4-dichloroaniline (7 mmol) were allowed to react in 2-methyltetrahydrofuran, a renewable and more eco-friendly solvent.⁷³ After 6 h, 5 mol% of the Ca catalyst and 1.2 equiv. of silane were added and the mixture was stirred for 24 h at 25 °C before achieving basic hydrolysis. ^1H NMR of the crude confirmed the complete conversion of both reactants, the absence of the intermediate imine and the quantitative formation of **2w**. The latter was isolated in 85% yield after column chromatography, which is in the same order of magnitude as on the

1 mmol scale from imine **1w** (90%, Fig. 1). It is worth noting that for this substrate, the amount of the catalyst could be decreased from 10 to 5 mol% and the excess of silane from 2 to 1.2 equivalents, while maintaining good performance. Under these conditions, more than 1.4 g of the expected amine could be obtained with high purity.

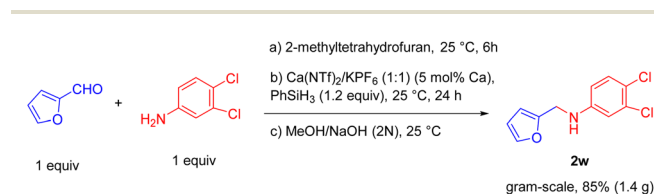
Conclusions

This method reports a simple and efficient method for imine hydrosilylation using a catalytic system based on non-toxic calcium, the fifth most frequent element in the Earth's crust. The proposed catalyst is based on $\text{Ca}(\text{NTf}_2)_2$ and KPF_6 , which act in a synergistic manner. Both precursors are readily available and easy-to-handle salts that can be stored on shelves, open to air and used for several months without loss of activity. This catalytic system is able to promote the hydrosilylation of a variety of aldimines under mild conditions (25–65 °C, 6–16 h) without requiring an inert atmosphere, and shows tolerance towards functional groups including halides (I, Br, and F), trifluoromethyls, ketones, esters or nitriles. The expected amines are obtained in fair to excellent yields.

The value of the method has been shown in the synthesis of a bioactive amine with antifungal properties, which was prepared on the gram scale and in high yield in environmentally friendly 2-methyltetrahydrofuran. It is shown in this example that the imine can be generated *in situ* from the corresponding aldehyde and amine without isolating the imine, which is interesting from a practical point of view. Overall, due to the nature of the metal (calcium is non-toxic even in large amounts) and the mild reaction conditions, the reported methodology contributes to the search for sustainable methods for the synthesis of amines, which are highly important building blocks in many fields. The resulting amines are free from traces of transition metals, which is of great interest in the field of pharmaceuticals, wherein metal contaminants are strictly regulated. No tedious and costly purification is thus needed. In addition, experimental data and DFT calculations are in accordance with an electrophilic Si–H activation pathway catalyzed by the $\text{Ca}(\text{NTf}_2)^+$ catalyst shown to promote imine hydrosilylation for the first time. To the best of our knowledge, such an electrophilic activation of the Si–H bond, well-known for boron catalysts, is not common in alkaline earth chemistry where an Ae–hydride complex is generally generated from calcium precursors and silanes through σ -bond metathesis (Scheme 1C). For the first time, $\text{Ca}(\text{NTf}_2)^+$ has been shown to activate Si–H bonds and studies to extend the scope of this catalyst to other challenging hydrosilylation reactions are currently underway.

Author contributions

Yougourthen Boumekla: investigation and methodology. Fengxie Xia: investigation. Lucas Vidal: investigation. Cédric



Scheme 3 Application of the method for gram-scale synthesis of an amine with anti-fungal activity.



Totee: methodology. Christophe Raynaud: methodology, software, formal analysis, and writing – review and editing. Armelle Ouali: conceptualization, methodology, writing – original draft, review and editing, and supervision.

Conflicts of interest

There are no conflicts to declare.

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