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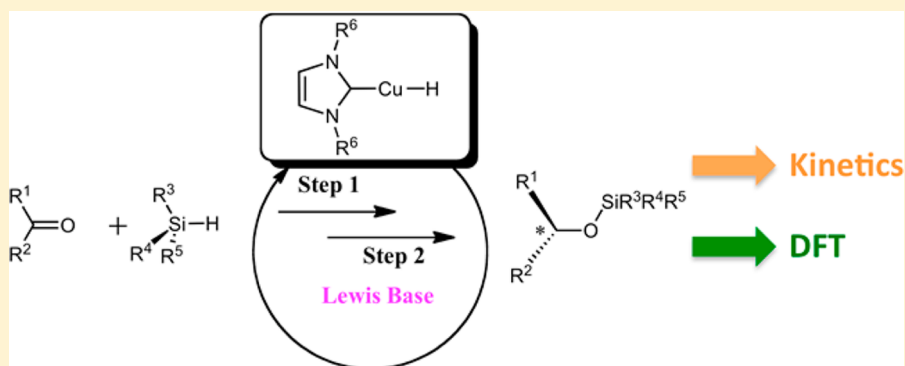
# Mechanistic Insight into the (NHC)copper(I)-Catalyzed Hydrosilylation of Ketones

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## Supporting Information



**ABSTRACT:** (NHC)copper(I) hydride catalyzed ketone hydrosilylation is an efficient method for the enantioselective synthesis of secondary alcohols. Herein, we represent a computational study of this reaction using density functional theory (DFT) on realistic model systems. This study is supported by kinetic investigations, using in situ FTIR measurements. The calculations validate the previously proposed reaction mechanism and explain the high activity of  $(OR^1)_xR^{2-x}Si-H$  types of silanes. Experimental evidence in favor of the monomeric (NHC)CuH form of the catalyst is also given. Combining experimental and theoretical results furthermore highlights a Lewis base activation of the hydrosilane, leading to a modified suggestion for the mechanistic scheme of the catalytic cycle.

## INTRODUCTION

Carbonyl bond reduction, specifically of aldehydes and ketones to the corresponding alcohol functionality via hydride transfer, is a fundamental transformation in organic synthesis.<sup>1</sup> Transition-metal catalysis has been successfully applied in the reduction of many carbonyl compounds via hydrogenation or hydrosilylation.<sup>1</sup> Hydrogenation reactions often proceed in good yield but require high pressure or elevated temperature. Moreover, if the reaction is part of a multistep synthesis, the resulting free alcohol frequently requires protection prior to the next synthetic step. In contrast, the softer reaction conditions of hydrosilylation turned out to be a major advantage, in addition to the fact that both the reduction and the protection steps are performed in a single, atom-efficient step.

Since the first catalytic hydrosilylation systems based on rhodium, developed in the early 1970s,<sup>2</sup> catalytic hydrosilylation of the carbonyl functionality was traditionally performed with precious, heavy metals ranging from Re, Rh, and Ru to Ir.<sup>3</sup> During the last two decades efforts were made to find efficient alternative systems using less expensive metals such as titanium,<sup>4</sup> iron,<sup>5</sup> manganese,<sup>6</sup> and zinc.<sup>7</sup> Since the first report of asymmetric hydrosilylation using a copper diphosphine catalyst in 1984,<sup>8</sup> many copper diphosphine catalytic

systems have been developed.<sup>9–11</sup> The active species formed in situ was postulated to be a copper(I) hydride. Lipshutz and co-workers describe the formation of the CuH species in a system combining a catalytic quantity of CuCl/NaOtBu/diphosphine and a stoichiometric quantity of hydrosilylating agent.<sup>12</sup> At the same time, Carreira and co-workers,<sup>13</sup> as well as Riant and colleagues,<sup>14</sup> reported CuF<sub>2</sub> systems as interesting precursors to copper hydride. Other air- and moisture-stable copper(II) salts, such as Cu(OAc)<sub>2</sub>, in combination with inexpensive and readily available diphosphines such as BINAP have been used efficiently to catalyze the hydrosilylation of various ketones.<sup>9c,15</sup> On the basis of these results, Wu et al. recently developed a highly asymmetric copper(II)-catalyzed hydrosilylation system.<sup>15b</sup>

N-heterocyclic carbene (NHC) ligands,<sup>16</sup> particularly of the type developed by Arduengo and co-workers,<sup>17</sup> have emerged as efficient ligands in metal-mediated reactions.<sup>18</sup> The majority of NHC ligands display electron-donating properties stronger than those of their phosphine counterparts,<sup>19</sup> leading to strong metal–ligand bonding, thereby minimizing ligand dissociation.

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tion.<sup>16,20</sup> This latter feature is particularly interesting when performing mechanistic studies, as this will simplify the system under study. A further advantage of the NHC ligands is a better steric protection of the active site within the inner metal's coordination sphere, because the exocyclic nitrogen substituents of the fan-shaped NHC shield the metal center more efficiently than a tertiary phosphine does, with its cone angle pointing away from the metal center.<sup>19e,20b</sup>

NHC ligands were shown to be interesting alternatives to phosphines for the copper-catalyzed hydrosilylation of carbonyl compounds. While (IPr)CuCl (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) was an efficient catalyst for the hydrosilylation of unhindered ketones,<sup>21</sup> (ICy)CuCl (ICy = 1,3-bis(cyclohexyl)imidazol-2-ylidene) and (SIMes)-CuCl (SIMes = 1,3-bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene) turned out to be effective for more challenging ketones.<sup>22</sup> The active species, formed in situ in the presence of a catalytic amount of NaOtBu and a stoichiometric quantity of hydrosilylating agent, is believed to be a copper(I) hydride. Yun et al. reported that copper(II) salts as catalytic precursors in combination with a NHC also lead to an effective hydrosilylation of ketones.<sup>23</sup> Recently, a series of cationic bis-carbenic complexes, [(NHC)<sub>2</sub>Cu]X (X = BF<sub>4</sub><sup>-</sup>,<sup>24</sup> PF<sub>6</sub><sup>-</sup>,<sup>24</sup> FHF<sup>-</sup><sup>25</sup>), has shown remarkable activity toward the hydrosilylation of ketones. Although once again the reaction pathway was not investigated, monocarbenic intermediates are believed to be the active species. Interestingly, the first asymmetric (NHC)-copper(I)-catalyzed ketone hydrosilylation was only developed recently by Gawley and co-workers.<sup>26</sup>

In all of the aforementioned studies, the suggested mechanism is based on the catalytic cycle shown in Scheme 1,<sup>11,22,24b,27</sup> illustrated using an (NHC)copper(I) chloride complex. As the Cu–Cl bond cannot be cleaved in an efficient manner by a hydride source (such as silane), the complex needs

to be activated through ligand exchange, replacing chlorine with an alkoxide or a fluoride. Although originally the activation of these latter was believed to pass through a  $\sigma$ -bond metathesis transition state,<sup>28</sup> we recently showed that even the activation step was poorly understood and more complicated than expected.<sup>29</sup> Working on (NHC)CuFHF bifluoride complexes, we showed these latter species to be activated by the fluorosilane byproduct, forming a tight ion pair of the type [(NHC)Cu]<sup>+</sup>[SiF<sub>2</sub>R<sub>3</sub>]<sup>-</sup>, which easily yields the desired copper-(I) hydride catalyst.<sup>29</sup> The (NHC)CuH active species is then postulated to react with a ketone passing through a four-center transition state to form a copper alkoxide (step 1). In turn, the copper alkoxide undergoes a  $\sigma$ -bond metathesis with the hydrosilylating agent to regenerate the CuH complex and form the silyl ether product (step 2).

This mechanism is relatively similar to that proposed for the hydrosilylation of ketones catalyzed by copper(I) phosphine complexes,<sup>9c,10,11</sup> for which it was confirmed using computational and mechanistic studies.<sup>30</sup> In a similar approach, we recently showed the theoretical validity of the suggested catalytic cycle for the hydrosilylation of ketones using a (NHC)Cu<sup>I</sup> hydride catalyst.<sup>31</sup> As the main goal of this study was to verify the plausibility of the catalytic cycle, simplified systems were used. In the present contribution, we want to achieve a full picture of this hydrosilylation reaction, not only by studying realistic systems (presented in Scheme 4) from a theoretical point of view but also by combining these results with experimental data from mechanistic studies. By doing so, we validate the suggested reaction mechanism and clarify the discussion on the rate-limiting step, and furthermore we are the first to bring insight into the “true” role of the Lewis bases, such as KOtBu, which are often added to “activate” the precatalyst. Moreover, the experimental data yield insight into the ongoing discussion concerning the oligomeric nature of the (NHC)Cu<sup>I</sup> hydride complex in solution, showing this latter species to be monomeric.

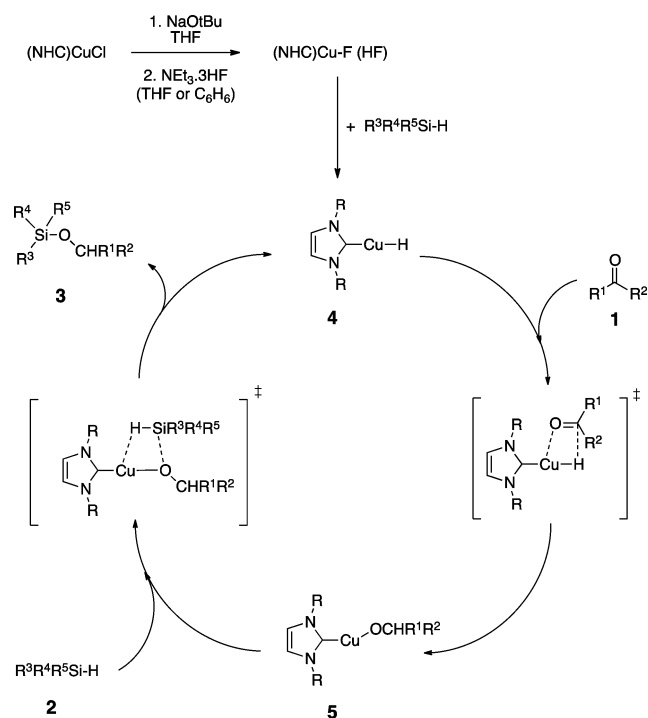
## RESULTS AND DISCUSSION

As mentioned above, we combine experimental mechanistic (mainly kinetic) studies with theoretical results to understand the full catalytic cycle. We start by using an (NHC)CuFHF autoactivating precatalyst<sup>29</sup> and Me(OEt)<sub>2</sub>SiH for the reduction of benzylacetone to verify the plausibility of the proposed cycle and to identify the rate-limiting step. To our surprise, the catalyst was no longer active when using trialkylsilanes. However, upon addition of KOtBu or NaOMe to the system, the catalytic activity was recovered. A second part of the discussion investigates the role of this base further, showing its active role within the catalytic cycle. Finally, our kinetic studies allow some insight into the oligomeric nature of the hydride catalyst in solution.

**1. Reactivity of the Reference (NHC)CuFHF/Me-(OEt)<sub>2</sub>SiH/Benzylacetone System.** At first we start by studying the reference system composed of (IPr)CuFHF catalyst (0.6 mol %), benzylacetone (1.0 equiv), and Me-(OEt)<sub>2</sub>SiH (1.02 equiv) as a hydride source, as this system leads to full conversion (>99%).<sup>25</sup> The proposed mechanism for this system is shown in Scheme 1. The kinetic rate expression corresponding to this scheme is developed in the Supporting Information with the main results shown in Table 1.

As shown by this table, the overall nonsimplified rate expression contains a two-term denominator (eq 1). In most

**Scheme 1. Suggested Cycle for the Asymmetric Hydrosilylation of Ketones using (NHC)copper(I) Catalysts**



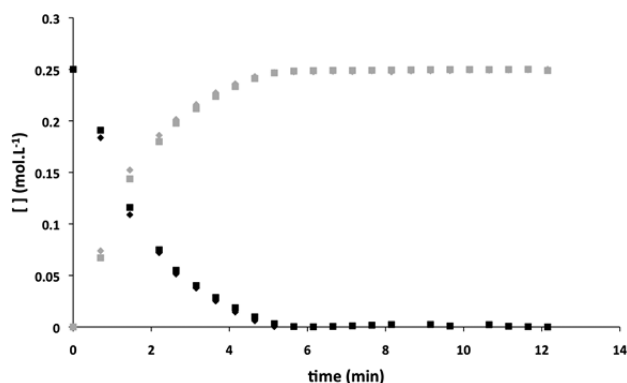
**Table 1. Full and Simplified Rate Equations Corresponding to the Catalytic Cycle Shown in Scheme 1<sup>a</sup>**

major Cu species (Scheme 1)	dominating term in denominator of eq 1	obsd rate eq	integrated rate eq
none	all terms contribute	$v = \frac{k_1 k_2 [1][2][Cu]^0}{k_1 [1] + k_2 [2]} \quad (1)$	
5	$k_1 [1]$	$v = k_2 [2][Cu]^0 \quad (2)$	$\ln\left(\frac{b^0 - x}{b^0}\right) = -k_2 [Cu]^0 t \quad (4)$
4	$k_2 [2]$	$v = k_1 [1][Cu]^0 \quad (3)$	$\ln\left(\frac{a^0 - x}{a^0}\right) = -k_2 [Cu]^0 t \quad (5)$

<sup>a</sup> $a^0$  and  $b^0$  represent the initial concentrations in ketone 1 and silane 2, respectively;  $[Cu]^0$  represents the total amount of catalyst within the system.

two-step catalytic cycles, one of the two rate constants is dominating and one of these terms can hence be neglected, leading to two extremes. In a first case, the second step is rate limiting with  $k_1[1]$  outweighing  $k_2[2]$ . This situation is commonly termed “saturation kinetics” in species 1, with a simplified rate equation being first order with respect to the silane 2 (eq 2 in Table 1). In the opposite case, the formation of intermediate 5 will be rate limiting, and the unbound catalyst species 4 is the “resting state” of the catalyst. The rate equation is now first order with respect to the ketone 1 (eq 3 in Table 1). If none of the terms dominates, the full rate equation (1) needs to be considered. Significant amounts of both 4 and 5 are present in the system. However, in this case, it is possible to force the system to one of the two limiting situations working with an excess amount of one of the reactants.

Figure 1 shows the data for the reference conditions (kin1 in Table 2: 273 K, 20 mL of toluene, 5 mmol of benzylacetone,

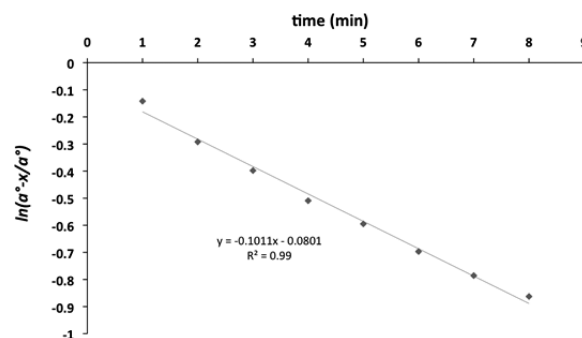


**Figure 1.** Concentration of reactant 1 (black) and product 3 (gray) over time under standard conditions (square and diamond points correspond respectively to two independent trials).

**Table 2. Experimental Plan Used Working under the Standard Conditions**

	ketone [1] (mol L <sup>-1</sup> )	silane [2] (mol L <sup>-1</sup> )	$k_x$ (L mol <sup>-1</sup> s <sup>-1</sup> )
kin1	0.25	0.26	$1.12 \pm 0.10$ ( $k'$ )
kin2	0.50	0.26	$5.44 \pm 1.01$ ( $k_2$ )
kin3	0.25	0.51	$2.59 \pm 0.87$ ( $k_1$ )

5.1 mmol of silane, 0.6 mol % of catalyst). Quantitative analysis is performed both on ketone reactant 1 and alcohol product 3, showing full conversion. As equal amounts of ketone 1 and silane 2 are considered, the full rate equation (1) reduces to  $v = k'[2][Cu]^0 = k'[1][Cu]^0$  with  $k' = k_1 k_2 / (k_1 + k_2)$ . Figure 2 shows a linearization of the data following the integrated



**Figure 2.** Linearization of the data of kin1 according to  $\ln(a^0 - x/a^0) = -k't$ .

equation. Considering an initial catalyst concentration of  $[Cu]^0 = 0.0015$  mol L<sup>-1</sup>, a value of  $k' = 1.12 \pm 0.10$  L mol<sup>-1</sup> s<sup>-1</sup> (confidence interval at 95%) is obtained. Although the observed data can be explained by the overall eq 1 it is possible that the system is in saturation kinetics with respect to either ketone 1 or silane 2. Two further trials were conducted, doubling the ketone or silane concentration (Table 2, kin2 and kin3) to verify if the system answers to one of the two extreme situations mentioned above (eq 2 or 3). To our surprise, the data of kin2 correspond to first-order kinetics in silane (eq 2), while the data of kin3 correspond to first-order kinetics in ketone (eq 3). The data of kin1 do not correspond to first-order kinetics in ketone (eq 3), nor do the data of kin3 to first-order kinetics in silane (eq 2) (see Figures S1–S6 in the Supporting Information). This implies that, when with an excess amount of ketone is used, step 2 is rate limiting, while when an excess amount of silane is used, step 1 becomes rate limiting. Such behavior was observed previously for diphosphine ligands<sup>30f</sup> and implies that both rate constants are of similar magnitude. Table 2 shows the rate constants obtained on the basis of the data of kin2 and kin3 and confirms similar rate constants for both elementary steps. Furthermore, they lead to a  $k'$  value of  $1.76 \pm 0.75$  L mol<sup>-1</sup> s<sup>-1</sup>, which is close to the value observed above (kin1).

To confirm the kinetic data, DFT simulations were made for both steps of the catalytic cycle. Table 3 shows the relative energies, enthalpies, and free energies of the species involved in the first step of the cycle for a variety of ketone species and NHC ligands (Scheme 4). As shown by this table, for the reaction to take place, free energy barriers ranging from 12 to 26 kcal mol<sup>-1</sup> with respect to the isolated reactants have to be overcome. Table 3 shows that the activation barrier strongly depends on the nature of the ketone ligand, with increases of 10.0 and 13 kcal mol<sup>-1</sup>, respectively, for acetone and benzophenone in comparison to the formaldehyde, and not

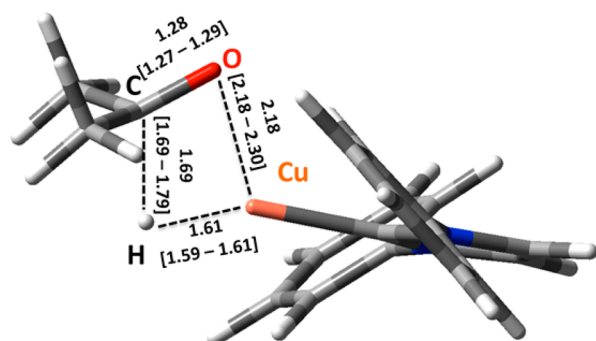
**Table 3.** Relative Energy ( $\Delta E$ ), Enthalpy ( $\Delta H^\circ$ ), and Free Energy ( $\Delta G^\circ$ )<sup>a</sup> with Respect to Isolated (NHC)CuH and R<sup>1</sup>R<sup>2</sup>CO Reactants during the First Step of the Catalytic Cycle<sup>a</sup>

NHC	R <sup>1</sup>	R <sup>2</sup>	TS $\Delta E$ ( $\Delta H^\circ$ ; $\Delta G^\circ$ )	product $\Delta E$ ( $\Delta H^\circ$ ; $\Delta G^\circ$ )	$\Delta E_{\text{int}}$	$\Delta E_{\text{strain}}(\text{catalyst})$	$\Delta E_{\text{strain}}(\text{carbonyl})$
ItBu	H	H	0.9 (2.2; 12.9)	−33.8 (−28.6; −18.7)	−11.8	3.6	9.6
	Me	Me	9.5 (10.1; 23.0)	−23.2 (−19.3; −6.7)	−8.1	3.7	13.9
	Me	Ph	14.3 (14.6; 26.4)	−19.3 (−15.1; −3.8)	−3.7	4.1	14.0
IPh	H	H	−0.8 (0.5; 12.1)	−34.1 (−29.0; −18.7)	−12.7	2.8	9.5
	Me	Me	7.7 (8.3; 22.1)	−23.8 (−19.3; −6.7)	−9.8	3.3	14.2
	Me	Ph	12.7 (13.0; 25.5)	−18.8 (−14.7; −3.8)	−4.9	3.4	14.3
IMes	H	H	−2.4 (−0.9; 13.1)	−34.4 (−29.3; −19.4)	−12.9	2.0	8.9
	Me	Me	6.0 (6.8; 23.0)	−24.3 (−19.7; −7.6)	−10.2	2.5	13.8
	Me	Ph	11.8 (12.1; 25.6)	−19.1 (−14.9; −3.6)	−5.6	2.9	14.4
IPr	H	H	−2.0 (−0.7; 12.4)	−34.6 (−29.7; −19.6)	−15.4	4.5	9.3
	Me	Me	6.3 (7.0; 22.3)	−25.1 (−19.5; −5.7)	−10.4	3.5	13.2
	Me	Ph	11.9 (12.2; 26.2)	−18.9 (−14.8; −2.6)	−6.1	4.6	13.4

<sup>a</sup>Interaction energies ( $\Delta E_{\text{int}}$ ) and strain energies ( $\Delta E_{\text{strain}}$ ) are also given. All values are in units of kcal mol<sup>−1</sup>.

on the nature of the NHC ligands considered here.<sup>32</sup> To explain the variations in activation barrier, electronic and steric effects were investigated.

Structurally, the transition states vary little when substituting the hydrogen atoms of formaldehyde by methyl or phenyl groups (Figure 3 and Table S1 (Supporting Information)). The

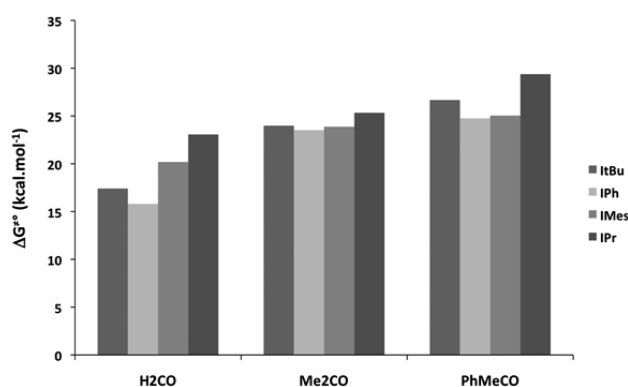


**Figure 3.** Transition state structure for the reaction between (IPh)CuH and Me<sub>2</sub>CO. Bond lengths are given in Å. The ranges of bond lengths observed for the different transition states studied are given in brackets (Table S1 (Supporting Information)).

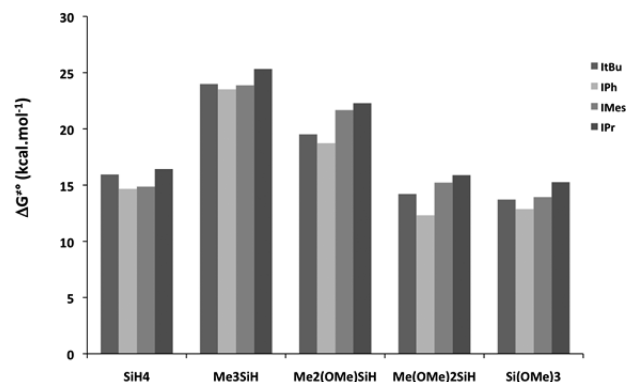
variation in activation barrier is therefore expected to be due either to variations in steric hindrance, or variations in interaction between the two reactants (electronic effect). The former will be assessed studying the strain energies ( $\Delta E_{\text{strain}}$ ), while the latter will be evaluated studying interaction energies ( $\Delta E_{\text{int}}$ ; these are defined in the Experimental and Computational Section). As shown in Table 3, the strain energy increases with the size of the ketone. The total strain energy increases by about 5 kcal mol<sup>−1</sup> for Me<sub>2</sub>CO and about 6 kcal mol<sup>−1</sup> for PhMeCO. This increase is mainly (80%) explained by the deformation of the carbonyl group. The increase in strain energy for the larger ketone systems is furthermore accompanied by a reduced interaction energy, which is likely explained by an increased electronic repulsion between the different functional groups (see Figures S7 and S8 (Supporting Information)).

As for the previous step, the second step of the catalytic cycle passes through a  $\sigma$ -bond metathesis four-center transition state.<sup>31</sup> All of the systems studied above were coupled to the series of silanes shown in Scheme 4, leading to a total of up to 60 simulations. The relative energies, enthalpies, and free

energies are presented in the Supporting Information (Tables S2–S4) and are given graphically in Figures 4 and 5 for the



**Figure 4.** Relative free energy  $\Delta G^\ddagger$  with respect to isolated (NHC)CuOCHHR<sup>1</sup>R<sup>2</sup> and Me<sub>3</sub>SiH reactants for the second step of the catalytic cycle. Values are given in units of kcal mol<sup>−1</sup>.



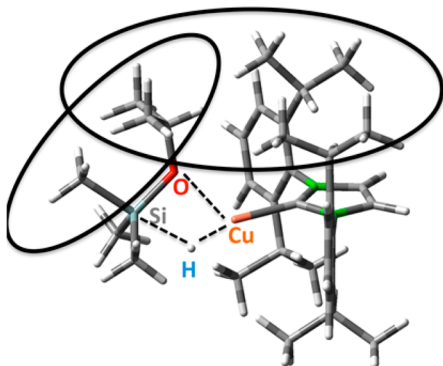
**Figure 5.** Relative free energy  $\Delta G^\ddagger$  with respect to isolated (NHC)CuOCHHMe<sub>2</sub> and R<sup>1</sup>R<sup>2</sup>R<sup>3</sup>SiH reactants for the second step of the catalytic cycle. Values are given in units of kcal mol<sup>−1</sup>.

systems containing respectively Me<sub>3</sub>SiH and acetone (see Figures S9–S14 (Supporting Information) for the other systems). As shown by these figures, the free energy barriers strongly depend on the nature of the silane species, as well as that of the carbonyl species.

Figure 4 shows an increase of up to 10 kcal mol<sup>−1</sup> for the larger carbonyl species. Structurally, the transition states do not

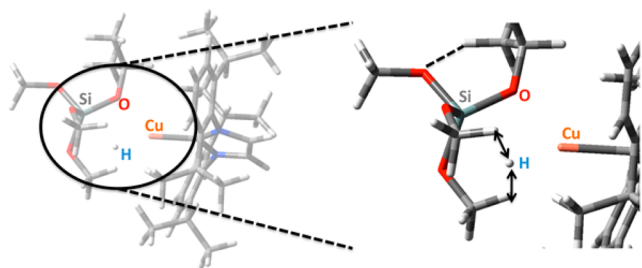


vary when the hydrogen atoms of formaldehyde are substituted by methyl or phenyl groups (Tables S5–S8 (Supporting Information)). This rise is due to steric repulsion occurring between these and the substituent groups of the NHC N-substituents (see a representative example in Figure 6). This fact is characteristic of the NHCs, as they are fan-shaped ligands.



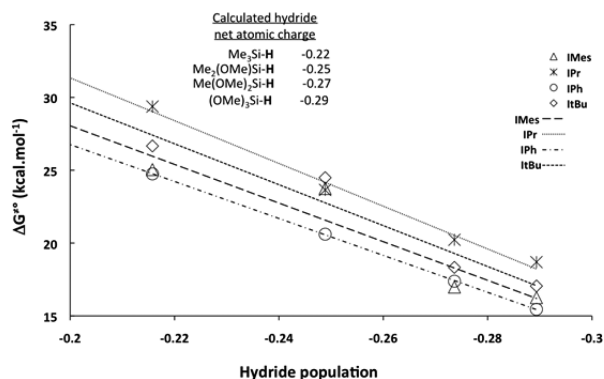
**Figure 6.** Transition state structure for the reaction between (IPr)CuOCH(CH<sub>3</sub>)<sub>2</sub> and (Me)<sub>3</sub>SiH. Zones where steric repulsion is expected to be important are highlighted with dark circles, while the dotted lines represent those bonds being broken or formed.

Figure 5 shows an even stronger effect of the silane species on the activation barrier in comparison to the effect of the carbonyl species discussed above. Steric repulsion occurs not only between the substituents of the silane species and the NHC N substituents but also between these silane substituents and the carbonyl function (Figure 6). If steric factors dominate, one would expect the larger (OMe)<sub>3</sub>SiH species to lead to the highest energy barrier, opposite to what is observed. Indeed, substitution of a –CH<sub>3</sub> group by a methoxy group on the silane significantly lowers the activation barrier (Figure 5). Mere steric effects are therefore no longer sufficient to explain the observed order of reactivity. Although some additional hydrogen bonding is observed for the (OMe)<sub>3</sub>SiH species in comparison to Me<sub>3</sub>SiH (Figure 7),<sup>33</sup> the hydride character of the silane species



**Figure 7.** Transition state structure for the reaction between (IPr)CuOCH(CH<sub>3</sub>)<sub>2</sub> and (OMe)<sub>3</sub>SiH. Acceptor–donor interactions are shown by double arrows, while the hydrogen bonds are indicated by dotted lines.

is the main factor explaining the variation in activation barrier. The Si–H bond polarization strongly increases with the number of substituting methoxy groups, leading to a more pronounced hydride character. This hydride character is directly related to the activation barriers, as shown in Figure 8. The effect outweighs all steric effects, and we can therefore



**Figure 8.** Hydride population dependence of the activation barriers of the reaction between (NHC)CuOCHH(Me)Ph and R<sup>1</sup>R<sup>2</sup>R<sup>3</sup>SiH. See Figures S15 and S16 (Supporting Information) for the formaldehyde and acetone systems, respectively.

conclude that, in contrast to the first step, the second step of the catalytic cycle is mainly under electronic control.

For the experimentally studied system, theoretical activation barriers of 21.2 and 26.2 kcal mol<sup>−1</sup> are observed for the second and first steps of the cycle, respectively. Although experimentally such differences should be observable, B3LYP theoretical precision on activation barriers is on the order of a few kcal. mol<sup>−1</sup>, which implies that such a small difference between barriers makes it difficult to theoretically proclaim a rate-limiting step. Experimentally, comparable rate constants for steps 1 and step 2 are observed. Furthermore, the calculated activation barriers of up to 30 kcal mol<sup>−1</sup> observed for the Me<sub>3</sub>SiH/acetophenone system (Figure S10 (Supporting Information)) could explain the reduced reactivity for trialkylsilanes, as observed experimentally. However, none of the above calculations is able to explain why these systems react when KOtBu is added.

**2. Effect of Lewis Bases.** As mentioned, relatively few hydrosilylation reactions with trialkylsilane are found in the literature.<sup>3–18,21–26,35,36</sup> When trialkylsilanes are used, either no reactivity is observed or heating to 60–100 °C is required. These observations can effectively be explained by the relatively high activation barriers of around 30 kcal mol<sup>−1</sup> observed for the Me<sub>3</sub>SiH species (see Figure S10 (Supporting Information)). However, when a catalytic amount of a Lewis base, e.g. RO<sup>−</sup> or F<sup>−</sup>, is present, the reaction seems to take place without any difficulty.

Most systems start from CuX (X = Cl, Br, I), and Lewis bases are required to activate the catalyst and are hence present in the reaction environment. However, in our case, the (NHC)-copper(I) bifluoride complexes used are autoactivating<sup>29</sup> and do not require addition of a Lewis base. The appearance of an intense yellow coloration upon addition of the silane confirms the creation of the active copper hydride species in solution. This yellow color usually remains until the end of the reaction. For the systems involving triethyl-, dimethylphenyl-, or dimethylbenzylsilane, the yellow coloration disappeared upon addition of the ketone species and no reaction occurred, even when the temperature was raised to 323 K. The disappearance of the yellow coloration is likely due to the occurrence of the first step of the catalytic cycle, forming the copper alkoxide intermediate, but the second step of the cycle does not take place due to the high activation barriers when these silanes are used.

Table 4. Kinetic Data for the Experimental Plan Used with 10 mol % of OMe<sup>−</sup>

	ketone [1] (mol L <sup>−1</sup> )	silane [2] (mol L <sup>−1</sup> )	[Cu] <sup>0</sup> (mol L <sup>−1</sup> )	[OMe <sup>−</sup> ] (mol %)	T (K)	k <sub>1</sub> (L mol <sup>−1</sup> s <sup>−1</sup> )	v <sub>i</sub> (mol L <sup>−1</sup> min <sup>−1</sup> )
kin4	0.25	0.25 <sub>5</sub>	0.0015	10	263	1.47 ± 0.13	0.0255
kin5	0.25	0.51	0.0015	10	263	1.09 ± 0.15	0.0226
kin6	0.50	0.25 <sub>5</sub>	0.0015	10	263	1.82 ± 0.21	0.0473
kin7	0.25	0.25 <sub>5</sub>	0.0015	10	253	0.680 ± 0.091	0.0161
kin8	0.25	0.25 <sub>5</sub>	0.0015	10	273	3.43 ± 0.46	0.0679
kin9	0.25	0.25 <sub>5</sub>	0.0030	10	273	3.01 ± 0.38	0.134

However, to our astonishment, as soon as KOtBu (10 mol %) was added to the system, the yellow coloration reappeared and full conversion was achieved in 10–30 min (the concentration profiles are presented in Figures S17–S19 (Supporting Information)).<sup>37</sup> This clearly shows that the Lewis base has an active role in the catalytic cycle.

To study this role further, we repeated the kinetic experiments, but with addition of a catalytic amount of OMe<sup>−</sup> (kin4, kin5, and kin6 in Table 4). All curves show an exponential decrease of the ketone concentration over time (Figures S20–S22 (Supporting Information)). Furthermore, plots of ketone conversion over time (eq 5,  $(a^0 - x)/a^0 = \exp(-k_1[Cu]^0 t)$ ) yield identical curves, which can be linearized taking the natural logarithm (Figures S23–S26 (Supporting Information)). These data relate to first-order kinetics in ketone 1, which is also confirmed by the initial rate<sup>38</sup> as presented in Table 4, with a doubled ketone concentration leading to a doubled initial rate. A doubled silane concentration, however, does not affect the initial rate, indicating zero-order kinetics with respect to [2]. In contrast to the results of the standard conditions (without addition of a Lewis base), the first step of the cycle has become the rate-limiting step (eq 5), with the copper hydride species 4 being the resting state of the catalyst, explaining the observed yellow coloration of the reaction environment. Considering an initial catalyst concentration of  $[Cu]^0 = 0.0015 \text{ mol L}^{-1}$ , an average value of  $k_1 = 1.46 \pm 0.16 \text{ L mol}^{-1} \text{ s}^{-1}$  (confidence interval at 95%) is obtained (Table 4). Finally, as shown by experiments kin8 and kin9, a doubled catalyst concentration leads to a doubled initial rate, indicating first-order kinetics with respect to the catalyst. The entire system thus corresponds to first-order kinetics in ketone and first-order kinetics in catalyst, indicative of the first step being rate limiting (eq 5).

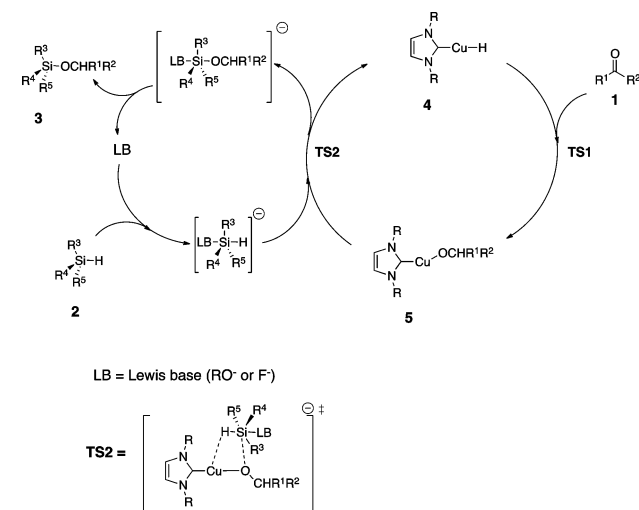
The activation energy for this step was determined at three different temperatures (kin4, kin7, and kin8). Using the Eyring equation, activation parameters were determined (see Figure S27 (Supporting Information)). The experimental activation enthalpy of  $\Delta H^\ddagger = 10.6 \text{ kcal mol}^{-1}$  is comparable to the computed value of  $12.2 \text{ kcal mol}^{-1}$  for NHC = IPr, (OEt)<sub>2</sub>MeSiH, and acetophenone (Table 3). A large activation entropy of  $\Delta S^\ddagger = -17.2 \text{ cal mol}^{-1} \text{ K}^{-1}$  is also found, as expected for a single concerted transition state formed from two reactant species.

On the basis of the above results, the Lewis base clearly allows reduction of the barrier of the second step. This means that this base either interacts with the silane species or exchanges with the copper alkoxide species. We showed that all copper alkoxide species show similar reactivities, hence leaving us with the first hypothesis. Indeed, the Lewis base activation of silanes to form pentacoordinate hydridosilicates is a well-established method for activating the silicon–hydrogen bond during the hydrosilylation of carbonyl compounds.<sup>39–41</sup> Organocatalysts formed this way can even work without any

transition-metal species.<sup>40g</sup> The reactivity of hypervalent silicon species is different from that of four-coordinated compounds, with increased electron density on all silicon-bound groups, hence increasing the hydride character.<sup>41,42</sup> Natural charge analysis of two model compounds, Me<sub>3</sub>SiH and [(OtBu)-Me<sub>3</sub>SiH]<sup>−</sup> at the b3lyp/6-31++G(d,p) level of theory shows hydride charges of −0.22 and −0.40, respectively. The hydride character of the pentavalent silicate is even more pronounced than that of the (OMe)<sub>3</sub>SiH species (−0.29), explaining the decrease in the step 2 activation barrier. We furthermore identified the backside S<sub>N</sub>2@Si transition state for the addition of OtBu<sup>−</sup> to Me<sub>3</sub>SiH (Figure S28 (Supporting Information)), leading to a trigonal-bipyramidal hydridosilicate, with the alkoxide and the hydride in apical positions. The computed free energy activation barrier of  $\Delta G^\ddagger = +4.8 \text{ kcal mol}^{-1}$  (Figure S26 (Supporting Information)) confirms our hypothesis of rapid interaction with the silane species, which then undergoes fast reaction in the catalytic cycle.

As the Lewis base is introduced in a catalytic quantity (10 mol %), a rapid exchange of the alkoxide between the R<sub>3</sub>Si(OR<sub>1</sub>)(OR<sub>2</sub>)<sup>−</sup> product species and R<sub>3</sub>SiH must occur for the reaction to go to completion. We thus suggest a modified mechanistic scheme (Scheme 2). In this scheme, the silane is

Scheme 2. Proposed Modified Mechanism for the Hydrosilylation of Ketones by Copper(I) Hydride Catalysts, Including Lewis Base Activation



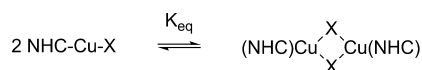
Lewis base activated, and step 2 still occurs through a  $\sigma$ -bond metathesis with a concerted transition state, between the copper alkoxide and the pentavalent hydridosilicate.

**3. Oligomeric Nature of the Copper Hydride Complexes.** Ever since Stryker's crystal structure of the phosphine-stabilized hexamer  $[(Ph_3P)CuH_6]$ ,<sup>9f</sup> an ongoing discussion has concerned the possibility of having different

oligomeric forms of copper hydride in solution. As NHCs are quite distinct from phosphines both electronically (through a stronger interaction with copper) and structurally (by providing a linear alignment between the carbene carbon, copper, and hydrogen atoms), a direct comparison with Stryker's reagent may be misleading. The minimized ligand dissociation and the significant steric bulk associated with the NHC family result in metal complexes having unique and distinct catalytic behavior in comparison to their phosphine-based analogues.<sup>21</sup> In the literature, examples of [(NHC)Cu]X complexes with a dimeric or even trimeric coordination mode in the crystalline state can be found, whereas in solution—to the best of our knowledge—only the existence of monomers has been reported so far. Moreover, the dimeric and trimeric structures include the participation of bridging halogenides—an unlikely behavior in the case of hydrides.<sup>43,44</sup> Additionally, only one set of signals was observed in the NMR spectra of those complexes, indicating either a fast exchange between the oligomeric forms in solution or a disaggregation of the solid structures, obtained at  $-40\text{ }^{\circ}\text{C}$ .<sup>9f,45</sup>

Our data argue in favor of a monomeric copper hydride form in solution. Scheme 3 presents the equilibrium between

**Scheme 3. Equilibrium between Monomeric (NHC)CuX and Dimeric [(NHC)CuX]<sub>2</sub> Complexes**



With: -X = H, Cl, F

- NHC = IPr, IMes, IAd (IAd = 1,3-bis(1-adamantylimidazol)-2-ylidene)

monomeric and dimeric (NHC)CuX complexes. The gas-phase equilibrium constant (Table S9 of the Supporting Information) suggests the existence of a monomer–dimer equilibrium for X = H, with values of  $K_{\text{eq}}$  on the order of 1–100 in favor of the dimer for the experimentally accessible NHC ligands (IPr, IMes, IAd). These values have to be viewed with some caution. In the gas phase, the entropic contribution to the free energy of the dimer is overestimated. This implies that the calculated  $K_{\text{eq}}$  values are also overestimated in favor of the dimer. In solution, the equilibrium is expected to be strongly shifted toward the monomeric form. In comparison, for the fluorine counterparts, calculated  $K_{\text{eq}}$  values are extremely high (on the order of  $10^9$ ), indicating a propensity to dimerize, even in solution, while in the case of the chlorine atom, only a monomeric form is expected (calculated  $K_{\text{eq}} \cong 10^{-4}$ ).

The kinetic data shown in this paper have the additional advantage that they yield insight into the oligomeric nature of the copper hydride species in solution. The equations shown in Table 1 were constructed under the hypothesis of a monomeric form being present in solution. When the first step is rendered rate limiting (e.g., with a Lewis base), first-order kinetics with respect to ketone and catalyst are expected, which is verified experimentally. If an equilibrium between monomeric and dimeric species exists, these kinetic equations are no longer valid, and we have to take this equilibrium into account (see the Supporting Information), leading to a novel expression for the kinetics as shown by eq 6. From eq 6, one clearly notices that in this case first-order kinetics with respect to the catalyst are no longer valid, in contrast to the experimental data, thereby yielding clear evidence of the copper hydride monomeric form in solution. To the best of our knowledge, this is the first

$$\nu = k_1[\mathbf{1}][\text{Cu-H}] = k_1[\mathbf{1}] \left( \frac{-1 + \sqrt{1 + 8[\text{Cu}]^0 K_{\text{eq}}}}{4K_{\text{eq}}} \right) \quad (6)$$

experimental proof of nonaggregated (NHC)CuH complexes in solution.

Furthermore, variable-temperature NMR experiments were conducted on the (IPr)CuH complex. In deuterated benzene, the copper hydride peak is identified as a singlet at 2.6 ppm.<sup>29,43</sup> If an equilibrium between monomeric and dimeric form exists, this signal can be expected to split at low temperatures. Spectra at  $-20$ ,  $-40$ ,  $-60$ , and  $-80\text{ }^{\circ}\text{C}$  in Tol-*d*<sub>8</sub> are presented in Figures S29–S31 (Supporting Information). No such peak splitting is observed, indicative of a single species present in solution. The small Cu–H peak broadening comes from the slower molecule motion with decreasing temperature (see Figure S32 (Supporting Information)).

## CONCLUSIONS

In summary, the mechanism of the copper hydride catalyzed ketone hydrosilylation was studied through kinetic investigations and DFT calculations on realistic systems. While the first step of the catalytic scheme is under steric control, the second step is shown to be mostly electronically governed. Our calculations highlight why an ethoxysilane of the type (OR)<sub>x</sub>R<sup>2</sup><sub>3-x</sub>SiH or PHMS and THMS are largely employed, as they are more reactive than their alkyl counterparts. Trialkylsilanes bring the second step activation barrier up to 30 kcal mol<sup>-1</sup>, in comparison to 17 kcal mol<sup>-1</sup> for the (OMe)<sub>3</sub>SiH species. Ethoxy groups enhance the hydride character of the hydrosilane, leading to a lower activation barrier for the second step of the catalytic cycle.

When a Lewis base, such as OR<sup>-</sup> or F<sup>-</sup>, is present in the reaction environment, a modified mechanistic scheme has to be taken into account. We showed that this base intervenes actively in the catalytic cycle, rendering the first step rate limiting, whereas the two steps are governed by similar rate constants in its absence. This change in behavior is due to an activation of the silane reactant.

Finally, we presented experimental evidence in favor of a full monomeric form of the (NHC)copper(I) hydride catalyst in solution.

## EXPERIMENTAL AND COMPUTATIONAL SECTION

**1. Computational Details.** Unless stated otherwise, all structures were fully optimized using Becke's three-parameter exchange functional<sup>46</sup> and the correlation functional of Lee, Yang, and Parr (B3LYP),<sup>47</sup> as implemented in the Gaussian 09<sup>48</sup> series of programs. All possible conformations have been investigated, and the most stable conformer is retained. Optimized geometries are provided as Supporting Information. Force constants were determined to characterize the stationary points, as well as to determine their entropies and free energies, on the basis of a statistical thermodynamics treatment. For the transition state (TS), the correctness of the curvature and its corresponding eigenvector were checked in order to guarantee the quality of the obtained results. Accordingly, in some cases, intrinsic reaction coordinate (IRC) calculations were performed to confirm that the transition state corresponds to the actual reaction mechanism.<sup>49</sup> In the continuity of our previous work,<sup>31</sup> the Cu atom was described using an effective core potential to represent all but the valence *nd* and (*n* + 1)*s* and outer core *ns* and *np* electrons.<sup>50</sup> The latter were described with a triple- $\zeta$  contraction of the original double-



$\zeta$  basis set; this combination is referred to as the LANL2DZ basis set. All nonmetal atoms were described using the polarized 6-31G(d,p) basis set.<sup>51</sup> When necessary, diffuse functions were added. Natural bond orbital (NBO) analysis was used to investigate electronic properties and charge distributions.<sup>52</sup> In our previous work,<sup>31</sup> we showed little dependence of the basis set and/or DFT functional on the results (calculations with 6-311G(2d,p) for all nonmetal atoms, def2-TZVP,<sup>53</sup> LANL2TZ(f),<sup>54</sup> and Stuttgart RSC 1997 ECP (SDD)<sup>55</sup> basis sets for Cu, and BP86,<sup>56</sup> B3PW91,<sup>46,57</sup> and MPW1PW91<sup>58</sup> functionals were used). In view of this result, and as the purpose of this study is to treat real, larger size systems, from a combined theoretical and experimental point of view, those calculations were not performed here.

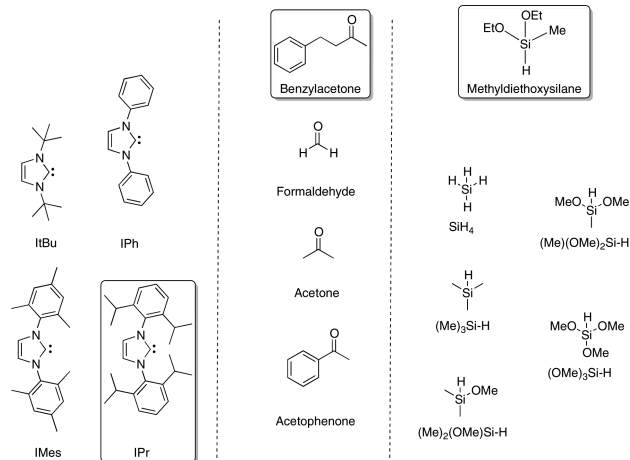
Strain energies ( $\Delta E_{\text{strain}}$ ) and the interaction energy ( $\Delta E_{\text{int}}$ ) are defined as shown in eqs 7 and 8, respectively, with  $E_{\text{react}}^{\text{TS}}$  being the reactant energy at the transition state geometry and  $n$  the number of reactants.

$$\Delta E_{\text{strain}} = E_{\text{react}} - E_{\text{react}}^{\text{TS}} \quad (7)$$

$$\Delta E_{\text{int}} = E^{\text{TS}} - \sum_{i=1}^n (E_{\text{react}}^{\text{TS}})_i \quad (8)$$

To arrive at the true catalytic system used experimentally (benzylacetone and methyl-diethoxysilane), the ketone and hydrosilane species are built up starting from formaldehyde and trimethylsilane, respectively, consecutively adding more complex functional groups (Scheme 4).

#### Scheme 4. Structure and Acronyms of NHC Ligands and Ketone and Silane Substrates Used Throughout This Work<sup>a</sup>



<sup>a</sup>The species shown in boxes are those used experimentally.

**2. Instruments, Chemicals, and Measurements.** Unless noted otherwise, all experiments were performed under an argon atmosphere using standard Schlenk-type glassware. Toluene was distilled on sodium under an argon atmosphere. Solvents used for workup were of technical grade. Commercial reagents were purchased from Acros, Sigma-Aldrich, ABCR, TCI, or Apollo Scientific and used as received unless stated otherwise, while (IPr)CuF and (IPr)CuFHF were synthesized following literature procedures.<sup>25,59</sup>

Time-resolved online ATR-FTIR spectra were recorded on a ReactIR 15 spectrometer (Mettler-Toledo) equipped with a zirconium probe with a resolution of 4 cm<sup>-1</sup> and 128 scans. Spectra were collected continuously at 1 min intervals. <sup>1</sup>H, <sup>13</sup>C, and <sup>29</sup>Si NMR measurements were carried out at 298 K on a Bruker Avance II 300 spectrometer equipped with a 5 mm BBFO probe z-gradient probe and/or on a Bruker Avance II 500 spectrometer equipped with a 5 mm

Broad Band z-gradient inverse probe. Column chromatography was carried out on silica gel (ROCC 60, 40–63 μm). TLC analyses were performed on commercial aluminum plates bearing a 0.25 mm layer of Merck Silica gel 60F254.

**3. General Procedure for the Reduction of Benzylacetone.** A flame-dried Schlenk was sequentially charged with a magnetic stirrer, the NHC copper complex (0.02 equiv), and freshly distilled toluene (4 mL per mmol). Methyl-diethoxysilane (1.2 equiv) was added dropwise, followed by the benzylacetone (1.0 equiv), and the mixture was stirred at room temperature. After total consumption of the starting material as indicated by TLC, TBAF (1 M in THF, 1.5 mL per mmol) was added and the solution was stirred for 15 min. The light gray mixture was filtered on a plug of silica gel (with PE/AcOEt 7/3 as eluent). Concentration in vacuo of the filtrate provided the desired alcohol (95–98% yield).

**4. General Procedure for the Kinetic Monitoring.** The general procedure is illustrated for an experiment having an equimolar mixture of ketone and silane reactants ([ketone]/[silane] = 1) but is similar for all other experiments. The reactor vessel was charged with a magnetic stirrer, the (NHC)copper (bi)fluoride complex (0.006 equiv), and freshly distilled toluene (20 mL). The vessel was then cooled to the required temperature, under a continuous nitrogen flow. At this stage hydrosilane (1.02 equiv) was added, leading to a yellow coloration of the solution, which was stirred for 10 min. Benzylacetone (5 mmol, 1.0 equiv) was then added and the reaction monitored by an in situ IR analysis. A continuous nitrogen flow was held throughout the entire duration of the experiment.

**5. IR Data Treatment.** All IR spectra are corrected by subtracting the solvent spectrum and using a baseline correction. Principal component analysis (PCA) and multivariate curve resolution (MCR) were used to extract the concentration profiles of reactants and products over time, using the The Unscrambler version 10.2 software (CAMO Software AS, 1986–2007). Kinetic orders with respect to reactants were obtained from an exponential fitting analysis of the concentration curves, varying the amounts of each component (ketone, silane, catalyst). Rate constants were obtained through linearization of the obtained data. For kinetic studies the quality of the obtained data is essential. For this reason, all conditions were repeated twice. Figure 1 shows the repeatability of the obtained data for ketone reactant and alcohol product concentrations over time under standard conditions.

## ■ ASSOCIATED CONTENT

### Supporting Information

Figures S1–S34 and Tables S1–S9 (as described in the text), text giving kinetic expressions, and a .xyz file of all computed molecule Cartesian coordinates for convenient visualization. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

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- (32) In contrast to what we found in our previous work,<sup>31</sup> there is no relation between step 1 activation barriers and the % $V_{\text{bur}}$  values of the NHC ligands considered in this study (see Figures S33 and S34 in the Supporting Information).
- (33) Hydrogen bonds between the oxygen of one of the methoxy groups and the hydrogen atom of a methyl group of the carbonyl show a NBO interaction<sup>34</sup> of about 1.9 kcal mol<sup>−1</sup> between the oxygen lone pairs and the  $\sigma_{\text{CH}}^*$  orbital of the methyl group (dotted lines in Figure 7). Another donor–acceptor type interaction of 3.6 kcal mol<sup>−1</sup> is found between two different hydrogen atoms of the methoxy groups and the hydride proton (Figure 7, double arrow).
- (34) For each donor (i) and acceptor (j), the stabilization energy  $E(2)$  associated with delocalization  $i \rightarrow j$  is estimated as  $E(2) = \Delta E_{ij} = q_i(F(i,j)^2)/(\epsilon_j - \epsilon_i)$ , where  $q_i$  is the donor orbital occupancy,  $\epsilon_i$  and  $\epsilon_j$  are the diagonal elements (orbital energies), and  $F(i,j)$  is the off-diagonal NBO Fock matrix element.
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