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Mechanistic study of catalytic copper-diaminocarbene (NHC) systems through computational *ab initio*, as well as experimental chemical studies

Abstract

The goal of this project is to fully characterize the mechanism of the (NHC)-Cu(I) catalyzed hydrosilylation reaction of carbonyls by experimental methods, kinetic studies and DFT calculations.

We first developed two synthetic pathways to unprecedented (NHC)Cu(I) bifluoride complexes and tested their catalytic activity in several known Cu(I) catalyzed reactions, demonstrating high catalytic activities. The self-activating mechanism of these (NHC) copper(I) (bi)fluoro pre-catalysts was then elucidated by a combined theoretical and experimental NMR study, showing bifluoride copper(I) complexes to be auto-activating catalysts. The plausibility of the catalytic cycle is subsequently investigated by a theoretical DFT study, on small model systems. Computations show both steps of the catalytic cycle to involve a 4 centre metathesis transition state. Finally, we present a detailed computational study of this reaction 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 $(OR^1)_x R^2_{(3-x)} Si-H$ type of silanes. Experimental evidence in favour of the monomeric (NHC)-Cu-H 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.

Keywords

N-heterocyclic diaminocarbene – copper(I) – DFT – hydrosilylation – catalysis

1. Introduction

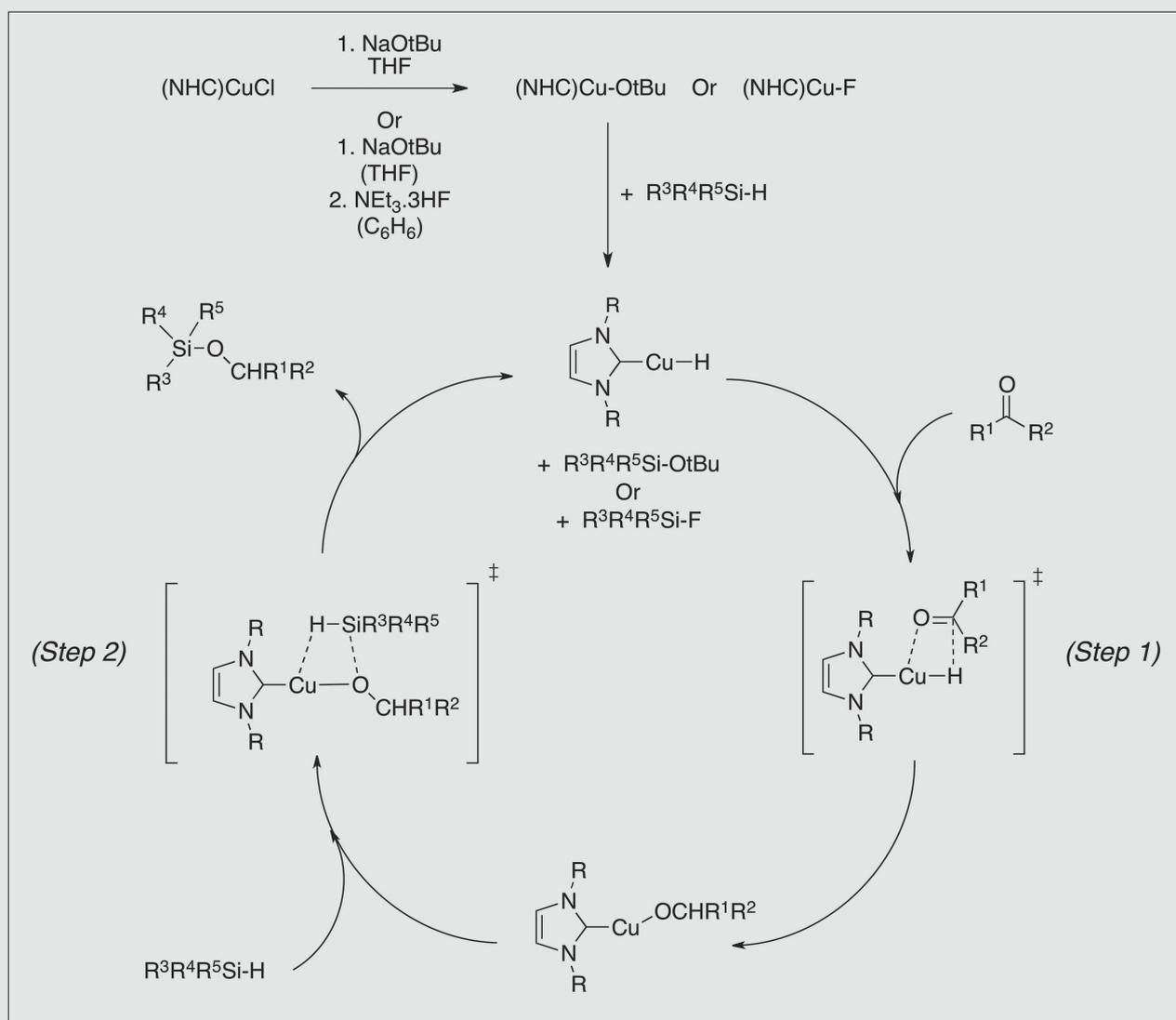
Metal-catalyzed hydrosilylation of carbonyls is a convenient reduction method and produces protected alcohols in one step under mild conditions [1-5]. Most industrial hydrosilylation applications use late transition metals, which are toxic and expensive. Thus, less expensive and more environmentally benign copper-catalysts form interesting alternatives [6]. The mechanistic schemes suggested for these metal catalysts share a common theme: the formation of a metal hydride intermediate upon the addition of silane followed by carbonyl insertion into the Cu-H bond to give an alkoxyde. Some metal hydride complexes have been obtained or observed under hydrosilylation conditions and were shown to be reactive. The question, however, remains whether they are the actual catalysts and what the true role of the hydride ligand is? Understanding how catalysis works is important for the rational design of new catalysts. Unfortunately, mechanistic data on copper-catalyzed hydrosilylation are scarce for diphosphine ligands and were non-existent for *N*-heterocyclic diaminocarbene (NHC) ligands; further investigations are thus required.

The goal of this project is to fully characterize the mechanism of the (NHC)-Cu(I) catalyzed

hydrosilylation reaction of carbonyls. The suggested mechanism is based on the catalytic cycle shown in Scheme 1 [7-11], illustrated using a (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 alkoxyde or a fluoride. The copper fluoride (or alkoxyde) complexes are then expected to be activated through a σ -bond metathesis reaction with a silane to yield the desired copper(I) hydride catalyst, thought to be the active species [12]. This active species is then postulated to react with a ketone passing through a four-centre transition state to form a copper alkoxyde (*Step 1*). Finally, the copper alkoxyde undergoes a σ -bond metathesis with the hydrosilylating agent to regenerate the Cu-H complex and form the expected silylether product (*Step 2*) [13].

These steps are supported by the isolation and the characterization of both complexes (the (NHC)-Cu(I) tert-butoxide or the NHC-Cu(I) fluoride and hydride complexes) [14]. (IPr)Cu-H (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) was indeed isolated as an unstable dimeric complex that readily reacts with a terminal alkyne to provide the corresponding hydrocupration product. Thus, it has been suggested that (NHC)Cu-H species agglomerate in solution, even if no experimental evidence of this agglomeration in solution is reported. This would imply that the equilibrium between monomeric and polymeric species is of prime importance for a complete understanding of the system under study.

This mechanism is relatively similar to the one proposed for the hydrosilylation of ketones catalyzed by phosphine copper(I) complexes [7, 15, 16], but does not explain why an excess of base is



Scheme 1: Proposed mechanism for the (NHC)-Cu(I) catalyzed hydrosilylation of ketones.

generally required in order to complete the reaction with (NHC)-based catalytic systems. As it is well known that hydrosilanes are prone to nucleophilic attack, recently Nolan *et al.* proposed that the excess base could be interacting with the hydrosilane to facilitate the second σ -bond metathesis [8, 11, 17].

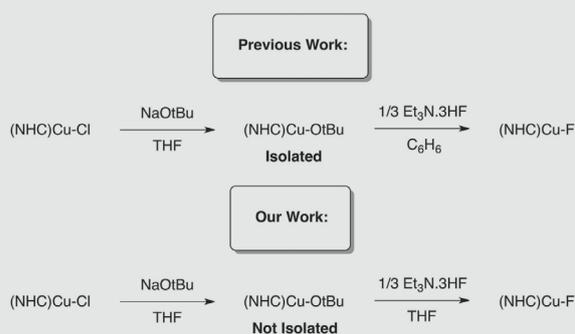
Some computational and experimental studies concerning the hydrosilylation reaction of ketones using copper(I) diphosphine complexes have been reported in the literature [18-22]. In those studies, step 2 is found rate-limiting, while the P-Cu-P bite angle is shown to control both the reactivity and the enantioselectivity. However, surprisingly no such studies were reported for (NHC)-Cu(I) complexes at the onset of this work.

The purpose of this work is thus to give mechanistic insight into this (NHC)-Cu(I) catalyzed hydrosilylation reaction of carbonyls by experimental methods, kinetic studies and DFT calculations. The multi-disciplinary approach presented here is not frequently encountered in catalytic chemistry, an area which could clearly benefit from such an approach due to the complexity of the systems. With this study, we try to illustrate the usefulness of such an approach (Scheme 2).

2. Unprecedented copper(I) bifluoride complexes [23]

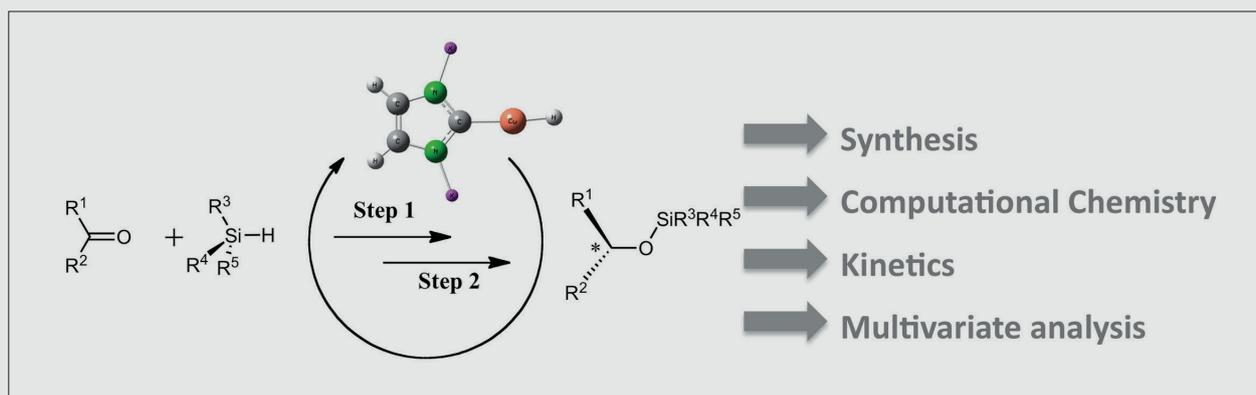
The first part of this project concerns the synthesis of the starting (NHC)-Cu(I) complexes, as well as establishing a quick and reliable method for their preparation. (NHC)Cu-F complexes were selected for this work to avoid use of sensitive and unstable complexes such as the (NHC)Cu-OtBu. To our knowledge, only five NHC copper(I) fluoride

complexes have been reported in the literature, available upon treatment of (NHC)Cu-OtBu with $\text{NEt}_3 \cdot 3\text{HF}$ (Scheme 3, top). Uniquely, these (NHC)Cu-F complexes are soluble in a wide range of organic solvents and demonstrate a high catalytic activity towards some transformations. The main drawback of these complexes stems from the high atmosphere sensitivity of the copper alkoxyde intermediates and copper fluoride adducts which requires glove box and strictly controlled Schlenk tube techniques for their preparation and handling. Various conditions were, therefore, tested to generate and react these intermediates without prior isolation (Scheme 3, bottom).



Scheme 3: Preparation of (NHC)Cu-F complexes.

Upon reacting (IPr)Cu-Cl with KOtBu followed by filtration under an inert atmosphere to remove KCl and addition of $\text{NEt}_3 \cdot 3\text{HF}$ without removal of THF, a new copper complex was isolated in a 75% yield. Single crystals were grown and X-ray analysis revealed an unprecedented (NHC) copper(I) bifluoride complex; (IPr)Cu-FHF (Figure 1). Crystals of (IPr)Cu-F were also grown, and the structure of both compounds was unambiguously shown to be different.



Scheme 2: Multidisciplinary approach used throughout this work.

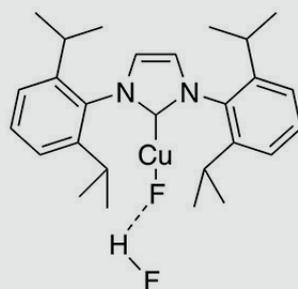
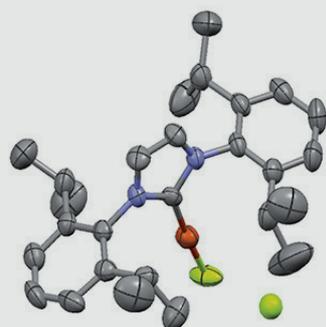
**(IPr)Cu-FHF**

Figure 1: X-Ray structure of (IPr)-Cu-FHF (CCDC nr. 849634). Selected bond lengths (Å), angles and torsional angles (°): Cu-F(1) 1.872, F(1)-F(2) 2.243, F(2)-F(1)-Cu 108.87, F(2)-F(1)-Cu-C 48.74 (Hydrogen atoms are omitted for clarity) [46].

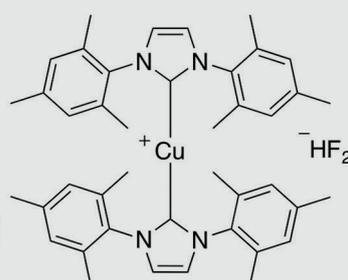
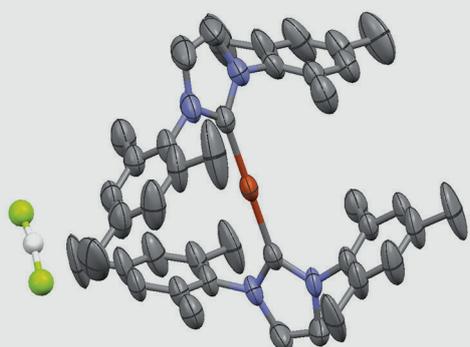
**[(IMes)₂Cu]HF₂**

Figure 2: X-Ray structure of [(IMes)₂Cu]⁺FHF⁻ (CCDC nr. 849633). Selected bond lengths (Å), angles and torsional angles (°): Cu-C 2.182, F(1)-F(2) 2.250, Cu-F(1) 6.490, C-Cu-C' 180.00, N(1)-C-C'-N(2) 60.04 (Hydrogen atoms are omitted for clarity) [46].

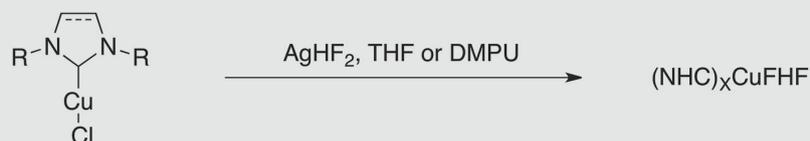
This new complex was fully characterized and unlike the corresponding (IPr)-Cu-F complex, proved to be highly air stable in the solid state and moderately stable in solution, with degradation occurring after two days.

The next step was to extend this new method to other NHC copper complexes. Remarkably, for the IMes ligand (IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene), similar reaction conditions led to the formation of an air stable bis(NHC) copper(I) complex [(IMes)₂Cu]⁺FHF⁻, structurally characterized by X-ray diffraction (Figure 2).

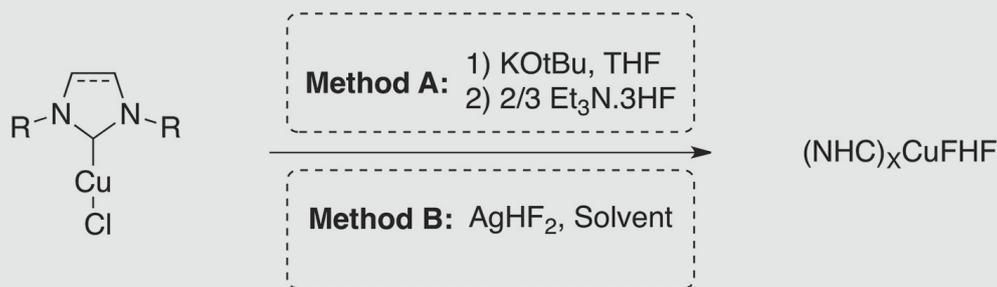
Encouraged by these initial results and looking to introduce chiral bifluoride complexes to our library, we sought to develop a more practical and convenient way of synthesizing these new NHC copper(I) bifluoride complexes. After numerous attempts, a general reaction pathway was established. As represented in Scheme 4,

reaction occurs directly between (NHC) Cu-Cl and AgHF₂. THF is the solvent of choice for the mono(NHC) complexes, while DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone) was preferred for the bis(NHC) complexes, due to its ability to solvate cationic metallic species.

With these two methods in hand, six new (NHC)_xcopper(I) bifluoride complexes were successfully synthesized (Table 1), two of these being chiral (NHC)copper(I) bifluorides ((IBP)Cu-FHF and (IBP*)Cu-FHF) based on the chiral NHC ligand family recently reported by Tomioka *et al.* [24]. Interestingly, the formation of either a (NHC)₂Cu-FHF or a (NHC)Cu-FHF bifluoride complex depends entirely on the nature of the NHC's R group, independent of the method used. Steric congestion around the metal centre is presumed to be the predominant factor.



Scheme 4: New synthetic route towards (NHC)_xCu-FHF (method B).



(NHC)CuCl	Method ^[a]	Solvent ^[b]	(NHC) _x CuFHF ^[c]	Yield(%) ^[d]
IPr	A (or B)	THF	IPrCu-FHF	75 (83) ^e
IMes	B	DMPU	[(IMes) ₂ Cu]HF ₂	60
SIPr	A (or B)	THF	SIPrCu-FHF	60 (50) ^e
SIMes	A (or B)	DMPU	[(SIMes) ₂ Cu]HF ₂	32 (85) ^e
(IBP)	B	THF	(IBP)Cu-FHF	64
(IBP*)	B	THF	(IBP*)Cu-FHF	Quant.

Table 1: Preparation of (NHC)_xCu-FHF complexes.

[a] Method A was run in THF under argon, method B was run in THF or in DMPU depending on the type of copper(I) bifluoride formed, under argon and in the dark [b] Solvent used in method B: THF for (NHC)Cu-FHF complexes and DMPU for (NHC)₂Cu-FHF complexes [c] The type of (NHC)_xCuFHF was determined by ¹⁹F NMR in accordance with the data of complexes 1 and 2 [d] Isolated yields [e] Isolated yields for method B.

With these complexes readily prepared and characterized, they were expected to show interesting catalytic activity due to the unique nature of the bifluoride counter-ion and the recent advances in (NHC)copper(I) catalyzed reactions [7, 10, 25-27]. For these reasons, the reactivity of these complexes was investigated in previously described copper(I) catalyzed reactions. Catalytic tests demonstrated these copper(I) bifluorides to be very efficient catalysts that do not require any additional activating agent. Doing so, we also established the first Cu-catalyzed diastereoselective allylation of (*R*)-*N*-*tert*-butanesulfinyl aldimines. The method enables efficient, simple and general synthesis of enantiomerically enriched homoallylic amines at room temperature in high yields. Although these results were very encouraging, no further reactions were explored as this would go behind the scope of this thesis.

3. (NHC)-copper(I) bifluoride complexes: "Auto-activating" catalysts [28]

Little to no attention was paid to the *in situ* formation of the actual copper hydride active species from the

(NHC)Cu-F pre-catalyst, as this process is assumed to occur through a σ -bond metathesis. However, from the surprising results *inter alia* mentioned above (*i.e.* no additional activating agent is required), this assumption seems unlikely. In this section we combine experimental NMR with computational results to elucidate the self-activating character of (NHC)Cu-FHF complexes, hereby shedding new light on the activation of (NHC)Cu-F complexes.

Experimental NMR studies show the activation of our (NHC)-Cu(I) bifluoride complexes to occur in two steps (Scheme 5). In a first step, gaseous hydrogen, one equivalent of fluorosilane and one equivalent of (NHC)-Cu-F are produced when reacting the (NHC) bifluoride complex with one equivalent of silane. The latter (NHC)-Cu-F is then expected to react with the second equivalent of silane, leading to the Cu-H catalyst, and a second equivalent of fluorosilane.



Scheme 5: The suggested reaction scheme to form (IPr)Cu-H from (IPr)Cu-FHF.

Combining these experimental results with computed NMR studies showed the fluorosilane by-product to activate the activation mechanism. Indeed, (NHC) Cu-F reacts with the fluorosilane, leading to a tight ion pair, between (NHC)-Cu(I)⁺ and a bifluorosilicate. This tight ion pair is expected to assist the hydride transfer from the hydrosilane to the copper atom. This allowed us to qualify these bifluoride species as “auto-activating” catalysts, with the activating agent, a fluorosilane, being created during the removal of the HF unit from the bifluoride pre-catalyst.

4. Plausibility of the mechanistic scheme [29]

In this section, the plausibility of the catalytic cycle suggested for the hydrosilylation of ketones by (NHC) copper(I) hydrides is investigated by a theoretical DFT study, investigating energetic, electronic and structural properties. As the goal is to verify the likelihood of the suggested cycle, small model systems are used.

Computations show both steps of the catalytic cycle to involve a 4 centre metathesis transition state as suggested in literature. These results show the reaction to be favoured by the formation of van der Waals complexes resembling the transition states. Stabilizing electrostatic interactions between those atoms involved in the bond breaking and bond forming processes induces the formation of these latter. Both steps of the actual catalytic cycle show a free energy barrier of about 14.5 kcal.mol⁻¹ for the largest NHC ligands, with respect to the isolated reactants, hereby confirming the plausibility of the suggested cycle (Figure 3). The large overall exothermicity of the catalytic cycle of about 35 kcal.mol⁻¹, is in agreement with experimental observations.

5. The total picture [30]

In this last chapter, the mechanism of the copper hydride catalyzed ketone hydrosilylation is studied through kinetic investigations and DFT

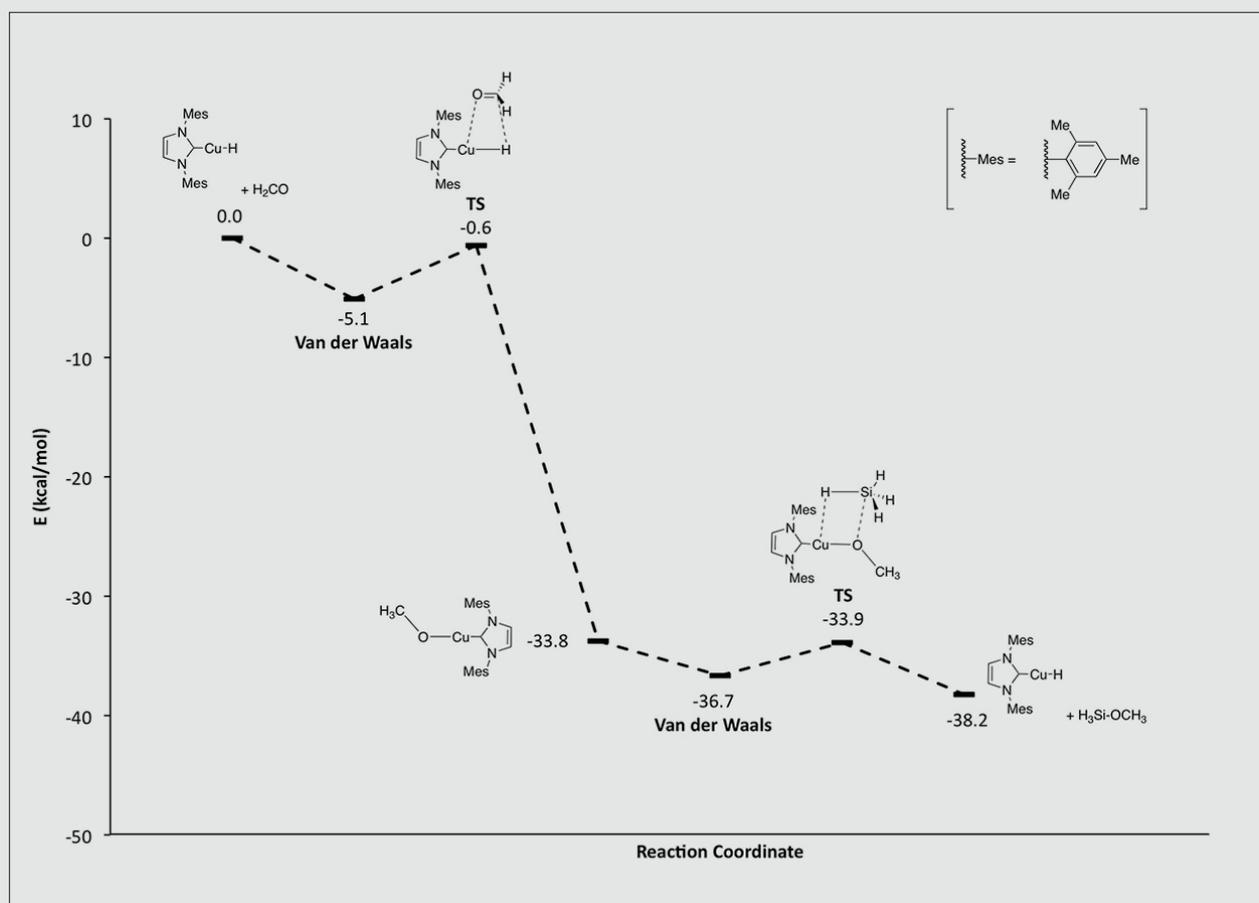


Figure 3: Calculated B3LYP/6-31++G(d,p) potential energy surface (kcal.mol⁻¹) for the catalytic cycle of hydrosilylation of formaldehyde by the (IMes)Cu-H catalyst.

calculations on experimentally used 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 ethoxysilane of the type $(OR^1)_xR^{2(3-x)}Si-H$ 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 $30 \text{ kcal}\cdot\text{mol}^{-1}$ compared to $17 \text{ kcal}\cdot\text{mol}^{-1}$ for the $(OMe)_3Si-H$ species. Ethoxy groups enhance the hydride character of the hydrosilane, leading to a lower activation barrier for the second step of the catalytic cycle.

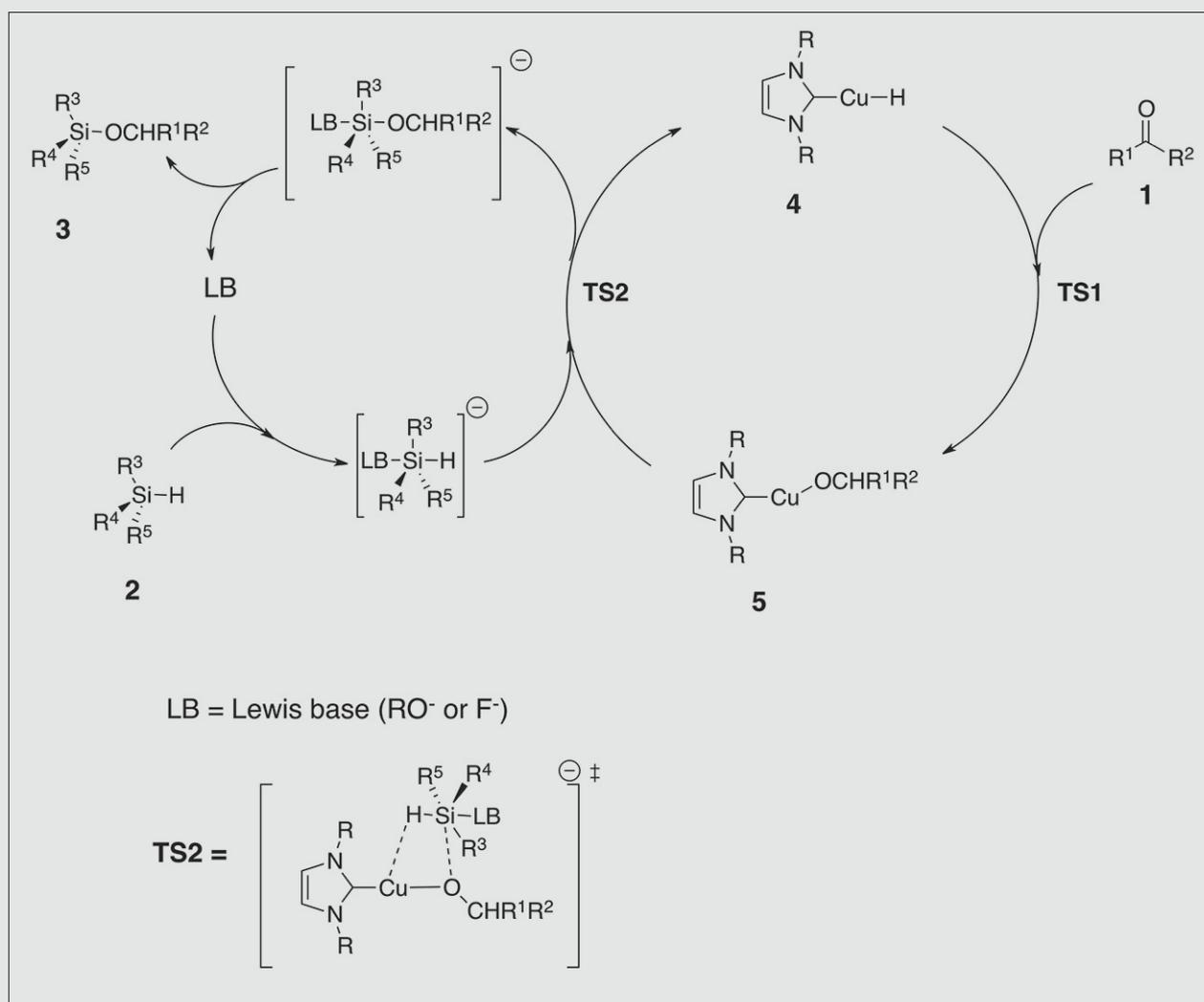
When a Lewis base, such as OR^- or F^- , is present in the reaction environment, a modified mechanistic scheme has to be taken into account. Through kinetics studies, we showed that this base intervenes actively in the catalytic cycle, rendering the first step rate-limiting, whereas the two steps are governed by

similar rate constant in its absence. This change in behavior is due to an activation of the silane reactant. We thus suggest a modified mechanistic scheme (Scheme 6). In this scheme, the silane is Lewis base activated, and step 2 still occurs through a σ -bond metathesis with a concerted transition state, between the copper alkoxyde and a pentacoordinate hydridosilicate.

Finally, we presented for the first time experimental evidence in favour of a full monomeric form of the (NHC)-copper(I) hydride catalyst in solution.

6. Conclusions

To provide some insights into the mechanism of NHC-copper(I) catalyzed hydrosilylation of ketones, we conducted a combined theoretical and experimental study.



Scheme 6: The proposed modified mechanism for the hydrosilylation of ketones by copper(I) hydride catalysts, including Lewis base activation.

To do so we decided to synthesize a small library of (NHC)Cu(I) fluoro pre-catalysts, which can be used for the mechanistic studies. We identified unprecedented (NHC)copper(I) bifluoride complexes and developed two synthetic pathways to obtain these.

We then analysed the activation step using experimental and computational NMR. This allowed us to qualify these species as ‘auto-activating’ catalysts, with the activating agent, a fluorosilane, being created during the removal of the HF unit from the pre-catalyst. We have furthermore shown the activation of the (NHC)Cu-F pre-catalysts to be more complex than the earlier suggested σ -bond metathesis.

In a second part of the mechanistic study, we verified the theoretical validity of the suggested catalytic cycle on small systems.

Finally, the last chapter tackles the true experimental system, from a computational and experimental (mainly kinetics) point of view. The influence of the NHC ligand, the ketone and the silane on the overall reactivity are discussed. Kinetics are used to verify the suggested mechanism, but also to determine the rate-limiting step. Evidence on the oligomeric nature of the copper hydride active species is also given. Furthermore, the combination of computational and experimental results demonstrated the Lewis bases true role in this catalytic reaction.

By combining experimental and theoretical results, a profound understanding of the mechanism of the (NHC)-Cu(I) catalyzed hydrosilylation of ketones is achieved, hereby demonstrating the usefulness of this kind of approach. We are convinced that theory and experiment should not be used as techniques *per se*, but are complementary to one another.

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