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Catching the Elusive Monomeric (L)CuH in NHC-capped Cyclodextrins (ICyDs) and Cavity-controlled Chemoselective Hydrosilylation of α,β-Unsaturated Ketones

Guangcan Xu,[a] Sébastien Leloux,[b] Pinglu Zhang,[a] Jorge Meijide Suàrez,[a] Yongmin Zhang,[a] Etienne Derat,[a] Mickaël Ménand,[a] Olivia Bistri-Aslanoff,[a] Sylvain Roland,[a] Tom Leyssens,*[b] Olivier Riant,*[b] Matthieu Sollogoub*[a]

[a] Sorbonne Université, CNRS, Institut Parisien de Chimie Moléculaire (IPCM), UMR 8232, 4, place Jussieu, 75005 Paris, France
E-mail: matthieu.sollogoub@sorbonne-universite.fr

[b] Institute of Condensed Matter and Nanosciences (IMCN) , Molecules, Solids and Reactivity (MOST), Université Catholique de Louvain (UCL), Place Louis Pasteur 1, 1348 Louvain-La-Neuve, Belgium
E-mails: tom.leyssens@uclouvain.be, olivier.riant@uclouvain.be

Abstract: The encapsulation of Copper inside a cyclodextrin capped with a N-heterocyclic carbene (ICyD) allowed both to catch the elusive monomeric (L)Cu-H and a cavity-controlled chemoselective copper-catalyzed hydrosilylation of α,β-unsaturated ketones. Remarkably, (α-ICyD)CuCl promoted exclusively the 1,2-addition, while (β-ICyD)CuCl produced the totally reduced product. The chemoselectivity is controlled by the size of the cavity and weak-interactions between the substrate and internal C-H of the cyclodextrin.

Encapsulating a metal center deep inside a well-defined cavity is a promising way to induce selectivities in chemical reactions and to stabilize highly reactive intermediates,[1] roughly imitating metallo-enzymes.[2] However, relatively few examples are reported in the literature where the cavity both includes the metal and is demonstrated to be responsible for the selectivity. Quite a few systems display the possibility to select a substrate over another, based mainly on steric hindrance around the metal induced by the cavity.[3] A few regioselective reactions are reported[4,5,6] with this kind of systems and here again the steric hindrance of the cavity governs the approach of the substrate and therefore the outcome of the reaction. Logically, chiral cavities have been used to induce enantioselective reactions.[7,8,9] Finally, an example where both enantio- and regio-selectivities are induced has been reported by Reek[10] for a hydroformylation reaction using an asymmetric container.[11]

Some of us developped N-heterocyclic carbene (NHC)-capped Cyclodextrin (CD) ligands called ICyDs, α-ICyD for the one derived from α-CD and β-ICyD for the one derived from β-CD.[7] (Fig. 1A) Functional CDs have been used as metal ligands before,[11,12] including by us,[13] but the singularity of the ICyD ligands is to place the metal center in the middle of the cavity and to force the substrate to be influenced by this cavity. We showed that the bridging induced a change in the morphology of the cavity introducing both an additional degree of asymmetry and different access to the metal depending on the nature of the CD (Fig. 1B). Hence, we could promote enantioselective gold-catalyzed cycloisomerisations,[7,8] and demonstrated that the shape of the cavity could change the regioselectivity of a copper-catalyzed hydroboration.[5,14]

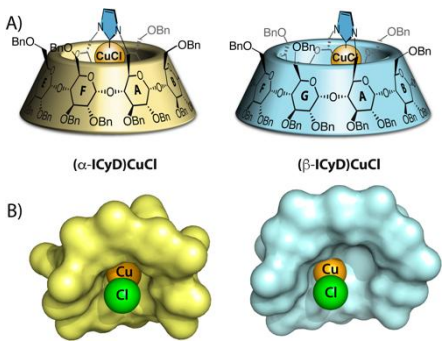
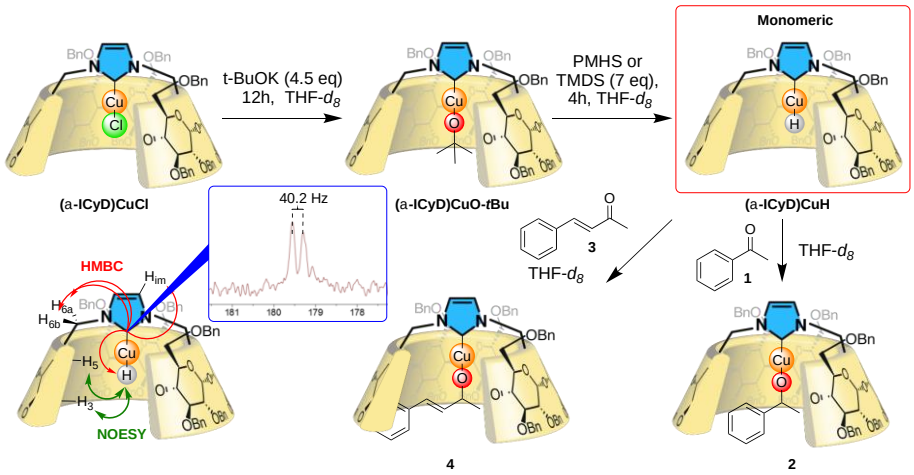


Figure 1. A) Structures of (α-ICyD)CuCl and (β-ICyD)CuCl; B) Shapes of the cavity of (α-ICyD)CuCl and (β-ICyD)CuCl

An archetypical and synthetically important chemoselective reaction that has not been studied with metals is the reduction of α,β-unsaturated ketone. Copper complexes are well-known catalysts promoting 1,4 addition of a hydride but very few examples

are reporting a 1,2 addition.[15] We therefore wondered if it was possible to force the system towards 1,2 addition thanks to the cavity of the ICyD ligand. The Osborn complex or Stryker's reagent $[(Ph_3P)CuH]_6$ is the first reported stabilized complex of a copper hydride, it is a hexamer,[16] and it was used in conjugate 1,4-hydrogenation of α,β-unsaturated ketones with high chemoselectivity.[17] Besides, a rare switching from 1,4 to 1,2-selectivity was observed by changing the ligand in this system.[18,19] However, the preparation, storage and use of this reagent is not straightforward. As an alternative, Lipshutz and Buchwald suggested to generate the active "Cu-H" species *in situ*, using a stoichiometric quantity of silane[20] with this reagent or a copper salt, a base and a ligand of choice to perform hydrosilylations allowing enantioselective reactions when using chiral phosphines ligands.[21] NHCs have also been used for chemo- and stereoselective 1,4-hydrosilylations.[22] There are also very few reports of 1,2-selective hydrosilylations. An enantioselective version was opened by Lipshutz[23] who initially showed that α-substitution of unsaturated ketones was needed to form secondary allylic alcohols. This substrate control of the 1,2 reduction over the 1,4 was further exemplified by Lipshutz with β,β-disubstituted enones,[24] and very recently by Mankad[25] and some of us[26] with α'-hindered ketones. By using a bulky and basic phosphepine ligand, Beller[27] described two examples of such selectivity, while a mixture of reduction products was observed when benzylideneacetone was used as substrate. Finally, Waidmann and Gordon showed one example of 1,2-selectivity.[28] Hence, the 1,2-selectivity of the copper-catalyzed hydrosilylation of α,β-unsaturated ketones is clearly dependent on the structure of the substrate, and particularly on the substitution of the double bond, but the bulkiness of the ligand also plays a role. This situation appeared perfect to test our system, as the sterics around the reactive Cu-H would be very well controlled and different in α- and β-ICyDs. We therefore embarked in the study of the cavity-dependency of the chemoselectivity of the hydrosilylation of α,β-unsaturated ketones using (ICyD)CuCl catalysts.

When dealing with CuH complexes a recurrent question turns around its nuclearity. Indeed, CuH complexes are usually oligomeric, and the monomeric Cu-H is notoriously elusive.[29] It was invoked by many, but never isolated and characterized on its own. Only recently, and for the first time, Bertrand spectroscopically described it in equilibrium with its dimeric form.[30] Owing to the high steric hindrance of α-ICyD, we performed the same study as Bertrand hoping to isolate monomeric CuH on its own at last. We followed the reaction by NMR, and first converted (α-ICyD)CuCl into its CuO*t*-Bu counterpart by action of *t*BuOK,[5] and then added 7 equivalents of polymethylhydrosiloxane (PMHS)[31] or of tetramethyldisiloxane (TMDS).[32] NMR indicated the formation of a single new product, identical with both silanes (see SI). The $^{13}C\{^1H\}$ spectrum showed a single carbene signal at 179.5 ppm, which appears as a doublet in the ^{13}C proton-coupled NMR, with a coupling constant of 40.2 Hz, characteristic of a trans $^2J(^{13}C\text{-}^1H)$ coupling, and already shown to be indicative of the monomeric copper hydride species.[30] HMBC experiment showed cross-correlations between the carbene C and protons of the imidazole ring, H6s of the sugars bearing the NHC and a proton at 1.5 ppm attributed to the hydride. Finally, NOESY experiment revealed through correlations between the hydride and intra-cavity H3s and H-5. (Scheme 1 and SI) We therefore isolated and spectroscopic characterized the elusive monomeric Copper-hydride, which appears remarkably stable in solution in the NMR tube for at least 48 h at room temperature. To probe its reducing activity, we first added acetophenone **1** and obtained the alkoxide **2** as expected. But much to our delight, when we added the α,β-unsaturated ketone benzylideneacetone **3** we obtained the product of 1,2-addition **4**. (Scheme 1)

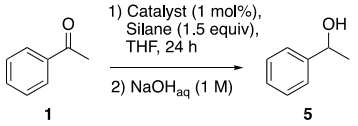


Scheme 1. Synthesis, characterization and reactivity of the monomeric CuH, (α-ICyD)CuH.

Initial experiments and optimization of the catalytic reaction parameters were carried out on the benchmark asymmetric reduction of acetophenone **1** to 1-phenyl-ethanol **5**,[33] using various ICyD-copper complexes (Table 1). Initially, the reaction was set up using (α-ICyD)CuF.HF (entry 1) which was designed to avoid the use of a co-catalyst such a metal alkoxide and facilitates the transfer of the hydride from silicon to copper to generate the copper hydride active catalyst.[34] However, with methyldiethoxysilane as a reducing agent, problems of reproducibility regarding both yields and enantiomeric excesses were observed. Moving to (α-ICyD)CuOH;[5] under the same conditions gave better conversion with increased ee's (entry 2). An additional important observation is that no additional base is required even when (α-ICyD)CuCl was used as a catalyst, and inert

atmosphere is not mandatory. To our knowledge, this is the first example in the literature where a CuCl catalyst is used without a base additive in hydrosilylation. With respect to the nature of the silane, $PhSiH_3$ led to excellent yields upon basic cleavage of the corresponding silyl ether (entries 2-5). Besides, when other silanes were used, lower conversions were observed (entries 7-13). For the remaining part of this study, phenylsilane was chosen as hydrosilylation agent. Finally, overall, β-ICyD gave similar yields but significantly lower ee's (entries 3, 6, 12). After optimization, (see SI) hydrosylations of ketones were carried out using 1 mol% of (α-ICyD)CuCl complex in THF at room temperature. Those conditions contrast with the previous ones as they implied use of an excess of base, low temperatures and inert atmosphere.[20-28] We then performed an exemplification of this reaction with various ketones using (ICyD)CuOH and (ICyD)CuCl affording ee's up to 91%. (see SI)

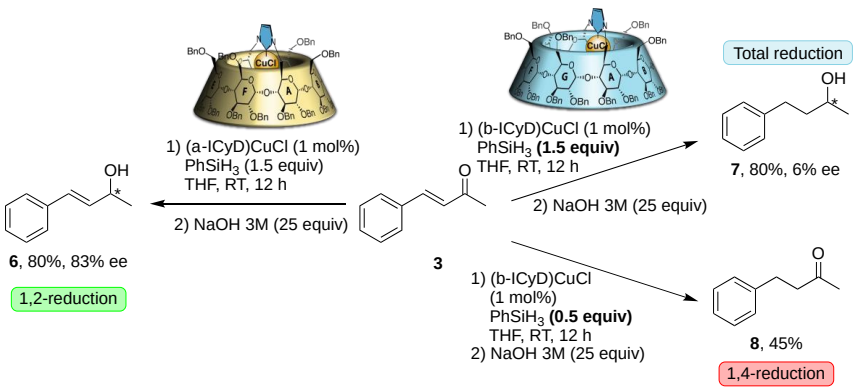
Table 1. Asymmetric hydrosilylation of acetophenone promoted by (α- or β-ICyD)Cu**X** complexes: effect of the NHC ligand and silane.



Entry	Catalyst	Silane	Conversion* (%)	ee (%)**
1	(α-ICyD)Cu**F.HF**	$Me(EtO)_2SiH$	60-95	14-42
2	(α-ICyD)Cu**OH**	$PhSiH_3$	100	86
3	(β-ICyD)Cu**OH**	$PhSiH_3$	100	55
4	(α-ICyD)Cu**F.HF**	$PhSiH_3$	100	86
5	(α-ICyD)Cu**Cl**	$PhSiH_3$	100	87
6	(β-ICyD)Cu**Cl**	$PhSiH_3$	100	54
7	(α-ICyD)Cu**OH**	Me_2PhSiH	14	83
8	(α-ICyD)Cu**Cl**	Me_2PhSiH	20	85
9	(α-ICyD)Cu**Cl**	$Me(EtO)_2SiH$	5	86
10	(α-ICyD)Cu**OH**	$Me(EtO)_2SiH$	65	72
11	(α-ICyD)Cu**Cl**	PMHS	4	85
12	(β-ICyD)Cu**Cl**	PMHS	11	55
13	(α-ICyD)Cu**Cl**	Ph_3SiH	0	-

* Conversion was determined using dimethyl terphthalate as internal standard ***ee* values were determined by GC analysis.

We next studied the hydrosilylation of α,β-unsaturated ketones using both (α- and β-ICyD)CuCl catalysts. We first looked at the reduction of benzylideneacetone **3**, which previously gave mixtures in that context.[27] This is a particularly challenging substrate as it is not functionalized in α, α' nor in β–β positions, which were shown to favor 1,2-reduction.[23-25] It is therefore particularly noticeable that we observed here a selective 1,2-reduction into allylic alcohol **6** when using the (α-ICyD)CuCl catalyst and a total reduction (1,2 and 1,4) of the α,β unsaturated ketone into **7** when using (β-ICyD)CuCl. (Scheme 2) If the 1,2 reduction with (α-ICyD)CuCl gave a respectable yield and enantiomeric excess, a dramatic drop in ee was observed when (β-ICyD)CuCl was used together with an increase of the yields in line with the reduction of ketones (see SI). Interestingly, when using only 0.5 equivalents of phenylsilane instead of 1.5 with (β-ICyD)CuCl, the ketone **8** resulting from the 1,4 reduction of **3** was observed with some starting material and no traces of alcohol **7** (Scheme 2). Hence total reduction of the α,β unsaturated ketone using (β-ICyD)CuCl, first operates in the expected 1,4 fashion, leading to the ketone, then an excess of silane affords the reduction of the carbonyl. However, when (α-ICyD)CuCl was used, no matter the quantity of silane only 1,2 reduction was observed.

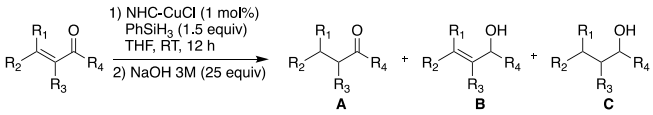


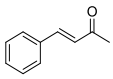
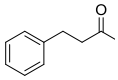
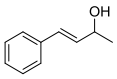
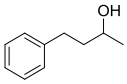
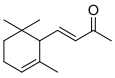
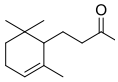
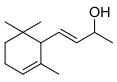
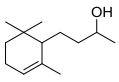
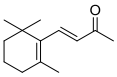
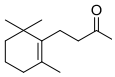
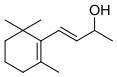
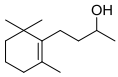
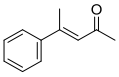
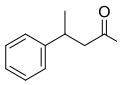
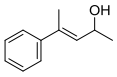
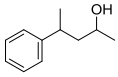
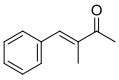
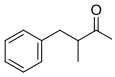
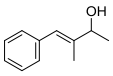
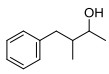
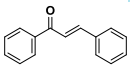
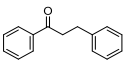
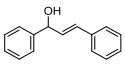
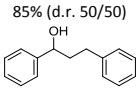
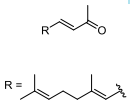
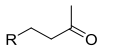
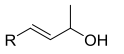
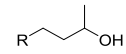
Scheme 2. Chemoselective hydrosilylation of benzylideneacetone with α- and β-ICyD complexes.

We then used this reaction on a range of α,β unsaturated substrates (Table 2). Various aromatic, cyclic and aliphatic α,β unsaturated ketones were tested with (α- and β-ICyD)CuCl as well as a benchmark (IPr)CuF.HF catalyst described elsewhere by some of us.[35] On the whole range of substrates complete chemoselectivity is observed only depending on the nature of the

catalyst. (IPr)CuF.HF always gave 1,4-reduction, (α-ICyD)CuCl operated the 1,2-reduction with variable enantiomeric excesses, and (β-ICyD)CuCl afforded the fully reduced compounds.

Table 2. Chemoselectvie hydrosilylation promoted by (α-ICyD)CuCl, (β-ICyD)CuCl and (IPr)CuF.HF complexes on various α,β unsaturated ketones.[a]



Substrate	Catalyst	A	B	C
				
	(IPr)CuF.HF	95%	n.d.	n.d.
	(α-ICyD)CuCl	n.d.	80% (83% ee)	n.d.
	(β-ICyD)CuCl	n.d.	n.d.	85% (6% ee)
				
	(IPr)CuF.HF	92%	n.d.	n.d.
	(α-ICyD)CuCl	n.d.	39% (10% ee)	n.d.
	(β-ICyD)CuCl	n.d.	n.d.	78% (n.d. % ee)
				
	(IPr)CuF.HF	82%	n.d.	n.d.
	(α-ICyD)CuCl	n.d.	52% (8% ee)	n.d.
	(β-ICyD)CuCl	n.d.	n.d.	85% (n.d. % ee)
				
	(IPr)CuF.HF	87%	0	0
	(α-ICyD)CuCl	n.d.	82% (59% ee)	0
	(β-ICyD)CuCl	n.d.	0	85% (d.r. 50/50)
				
	(IPr)CuF.HF	91%	0	0
	(α-ICyD)CuCl	0	95% (85% ee)	0
	(β-ICyD)CuCl	0	0	85% (d.r. 50/50)
				
	(IPr)CuF.HF	90%	0	0
	(α-ICyD)CuCl	0	54% (29% ee)	0
	(β-ICyD)CuCl	0	0	84% (51% ee)
				
	(IPr)CuF.HF	96%	0	0
	(α-ICyD)CuCl	0	68% (n.d. % ee)[a]	0
	(β-ICyD)CuCl	0	0	88% (n.d. % ee)[a]

Enantiomeric excesses were determined by GC or HPLC methods depending on the final alcohol. [a] Enantiomeric excess was not determined due to the presence of a mixture of isomers from the starting material.

We therefore observe a full control of the chemoselectivity of the reduction of α,β unsaturated ketone only relying on the size and shape of the cavity of the ICyD catalyst. To investigate in more details the reasons underlying this chemoselectivity through cavity control, we decided to performed a theoretical study using DFT calculations (B3LYP-D3/def2-SV(P), Turbomole V6.5). We first modelled both (α-ICyD)CuH and (β-ICyD)CuH together with benzylideneacetone **3**, then, we approached the hydride next to either position 2 or position 4 and reached two transition states in both cases, that gave the products of 1,2 or 1,4 addition respectively. In the case of (β-ICyD)CuH, the difference in energy of these TSs accounts for the preferential "natural" 1,4-addition. Rewardingly, in the case of (α-ICyD)CuH, the **TS-α-1,2** is significantly lower in energy than **TS-α-1,4** (Fig. 2).

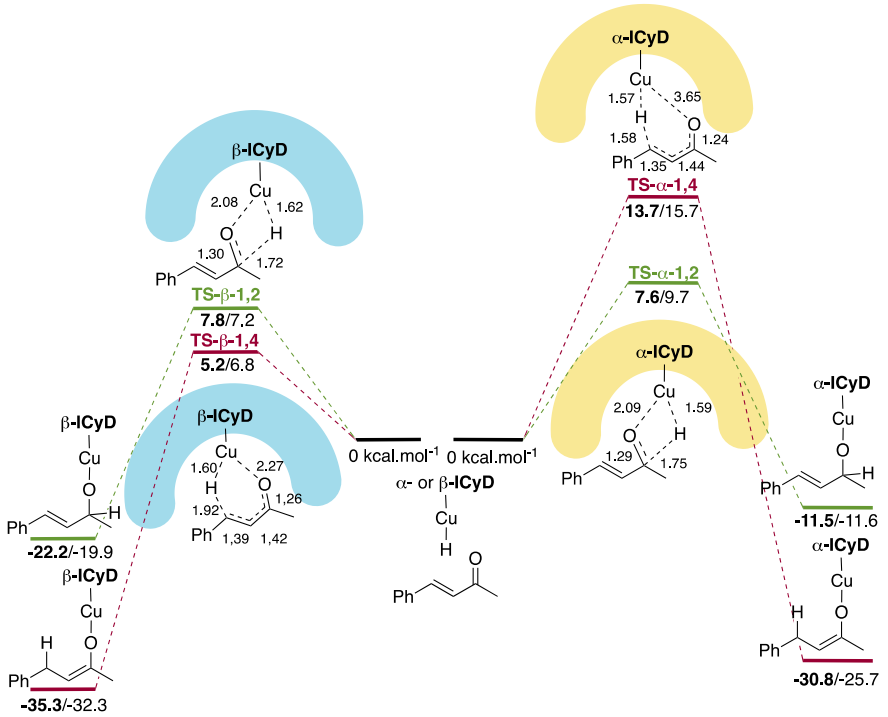


Figure 2. DFT calculated reaction pathways comparing the 1,2 and 1,4-addition on benzylideneacetone by a model of (α-ICyD)CuH and (β-ICyD)CuH. Distances between atoms are given in Å and enthalpies (in bold) and free energies in kcal.mol^{-1}

Only a few theoretical studies have been performed on regioselective hydrosilylations of α,β-unsaturated ketones.[24,25,36] In most of the cases, the 1,4 addition is obtained from the direct activation of the alkene.[24,36] This mechanism is precluded in our system, clearly for steric reasons, as the alkene does not have access to the copper. Therefore, the 1,4-addition requires the activation of the ketone.[25] Here, the difference between the two cavities appears, in **TS-α-1,4** the distance between the copper and the oxygen atoms is 3.6 Å, while it is 2.3 Å in **TS-β-1,4** (Fig. 2 and 3). Hence, the reaction is more concerted and easier in β-ICyD than in α-ICyD. This is certainly due to the differences of size and shape of the two cavities. In the case of (β-ICyD) there is more room for the ketone to interact with the metal, while in the α-ICyD the ketone does not have the space. This is also manifested by the different orientations of the ketone compared to the cavity on figure 3, it can enter the cavity in **TS-β-1,4**, while it stays flat at the entrance in **TS-α-1,4**. (Fig. 3, 4)

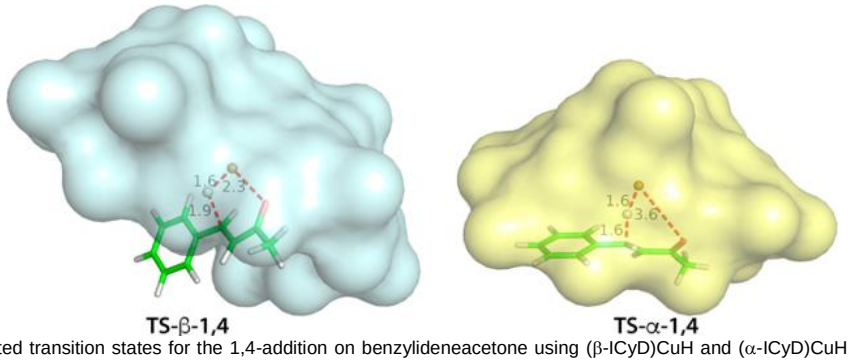


Figure 3. DFT calculated transition states for the 1,4-addition on benzylideneacetone using (β-ICyD)CuH and (α-ICyD)CuH. Distances between atoms are given in Å.

We then performed a NCI (Non-Covalent Interaction) analysis[37] on the TSs looking for additional weak interactions in these catalytic pockets, and we indeed detected attractive interactions between C-Hs of the CD and the carbonyl oxygen of the substrate. The activation of a C=O bond by a C-H has been rarely invoked,[38] usually with polarized C-H next to a quaternary ammonium[39] or in conjunction with another H bond.[40] For α-ICyD, this interaction is much stronger in **TS-α-1,2** than in **TS-α-1,4**. On the contrary, for β-ICyD, **TS-β-1,2** has one such interaction while **TS-β-1,4** has two (Fig. 4). So, while **TS-α-1,2** and **TS-β-1,2** very much look alike, **TS-α-1,4** and **TS-β-1,4** differ in many ways: only a weak hydrogen bond in the α-CD and two strong ones in β-CD. Furthermore, in the β-CD the interactions involve H-5s, which are situated deep inside the cavity. Hence, not only steric hindrance is at play but also attractive interactions with the cavity playing the role of second sphere of coordination. This

study clearly demonstrates that it is the morphology of the cavity that allows and favors 1,4-addition in the β-CD and precludes it in α-CD.

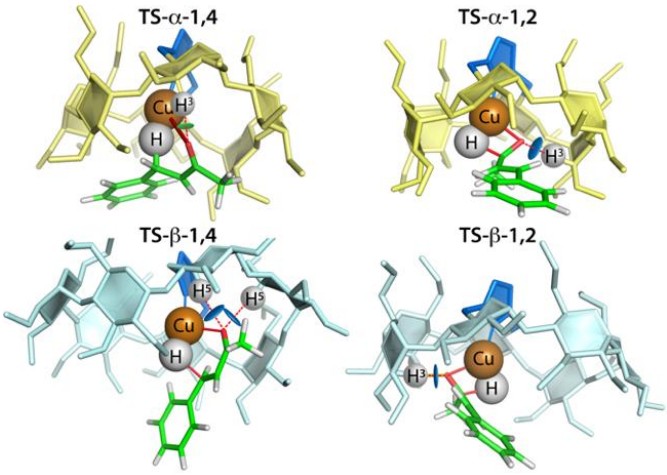


Figure 4. View of the two key transition states for each ICyD, highlighting the interaction between the substrate and the C

We were therefore able to induce chemoselective reductions of α,β unsaturated ketones only based on the structure of α- or β-ICyD ligands. Moreover, we were able to isolate a monomeric CuH inside the cavity which confers this very reactive species with remarkable stability. The difference in accessibility to the metal in both cavities is responsible for the difference in selectivity. Additional interactions with the cavity itself seem to favor 1,2-addition in α-ICyD and 1,4-addition in β-ICyD making this system even more enzyme-like.

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