Metallocavitands

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NHC-Capped Cyclodextrins (ICyDs): Insulated Metal Complexes, Commutable Multicoordination Sphere, and Cavity-Dependent Catalysis**

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Metal centers associated with cavities have attracted much attention, mainly because of their resemblance to metalloenzymes.[1] Among concave molecules with a cavity, cyclodextrins (CDs) are unique owing to their natural occurrence, their hydrosolubility, and the structure of their cavity. Unlike any other cavity, in particular those based on aromatic rings, their interior is carpeted with hydrogen atoms, which confer hydrophobicity and introduce additional van der Waals interactions. Therefore, CDs are widely used to host hydrophobic molecules in polar solvents. The possibility of converting cyclodextrins into enzyme mimics very soon attracted the interest of scientists.[2] More specifically, for CDs to be used to mimic metalloenzymes, a metal must be attached to the CD scaffold.[3] Owing to the size of the cavity, two different ways to append the metal can be considered for the study of two different phenomena. First, the metal can be positioned at the entrance of the cavity to exploit the inclusion ability of the cavity in its interaction with a substrate and mimic the binding pocket of an enzyme (Figure 1 a). Second, the metal can be encapsulated inside the cavity to study the effect of confinement on its coordination sphere and chemical properties; this arrangement mimics the environment of a metal buried deeply within a folded protein (Figure 1 b).

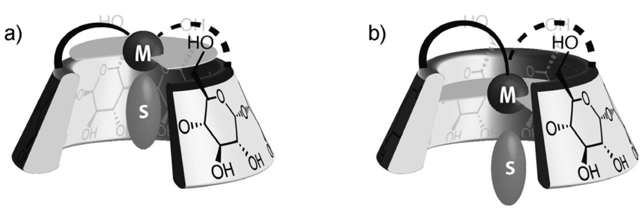

Figure 1. In a metal-capped cyclodextrin, the cavity interacts either a) with the substrate or b) with the metal, depending on the depth of inclusion.

The first kind of design has been widely studied, often with the attachment of a metal–ligand unit through a single linkage.[3] Such structures can be used in a multitude of applications, for example, in catalysis.[4] However, for the metal center to be fixed directly above the cavity, double linkage of the metal was necessary. In the resulting so-called metal-capped CDs,[5,6] the metal ion is located right on top of the CD cavity.[7] The deepest position in which the metal has been placed so far intercepts the plane defined by the C-6 atoms of the sugar units.[8,9] This metal position leaves the cavity available for the inclusion of guests. The cavity can thus serve as a host for substrates (the interaction of which with the metal center can lead to an acceleration of the reaction rate[10] in analogy with an enzymatic reaction), as a probe for ligand exchange,[8] or as a second coordination sphere through C−H···X−M interactions.[11]

For metallocyclodextrins of the second kind, in which the metal center occupies the middle of the cavity like an included guest, typically at the level of the H-5 atoms, only noncovalent inclusion complexes of metal ions have been described so far. Their electrochemical properties have been studied thoroughly, and electron transfer is thought not to involve the included complex, but the free portion of non-included metallic guest ions.[12] In other words, no studies on cyclodextrin complexes in which the metal ion is forced through covalent bonding to be included deep inside the

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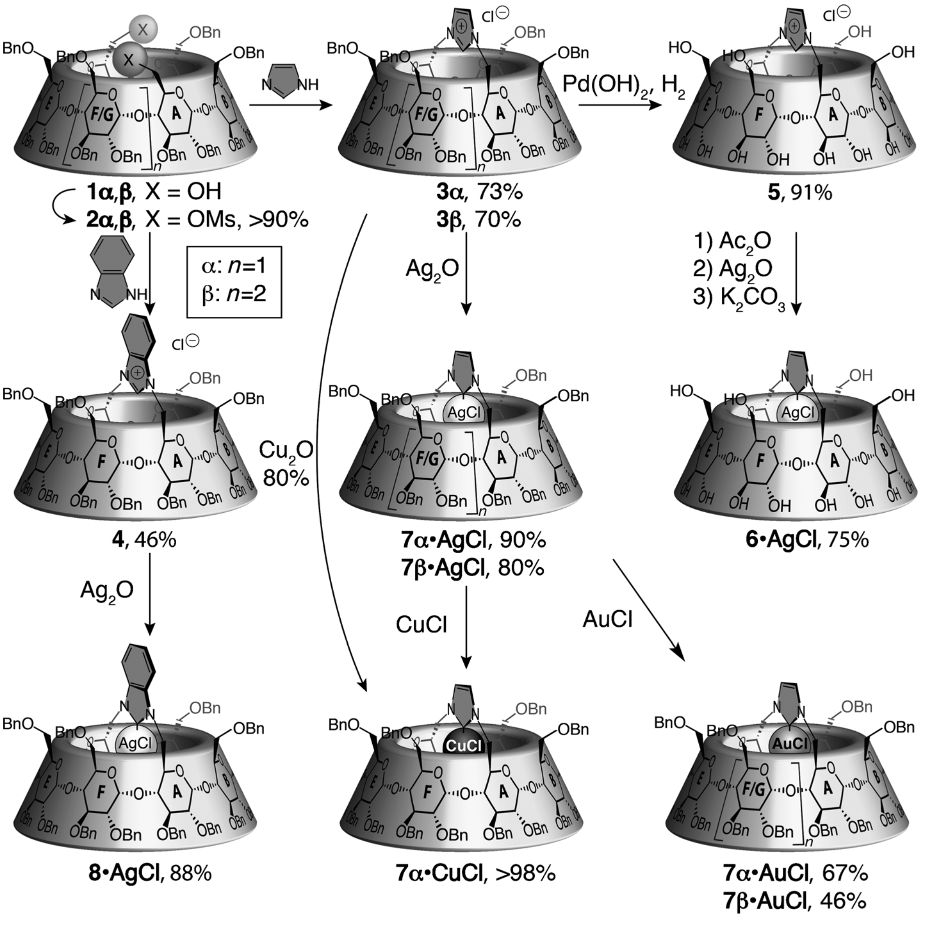
cavity have been reported so far. We present herein the synthesis of metallocyclodextrins with a metal atom embedded in the center of the cavity of the macrocycle, structural studies highlighting the novel coordination spheres of the metal, the electrochemical behavior of these complexes, and some aspects of their reactivity.

In the generation of a CD containing a metal ion in the middle of its cavity, we were helped by serendipity. During the course of our studies on CD-based ligands, we turned our attention from phosphines[13] to N-heterocyclic carbenes (NHCs)[14,15] and embarked on the synthesis of CDs functionalized with two diametrically opposed NHCs.[16] We made use of our previously developed approach to perbenzylated diols **1α** and **1β**,[17] which were subsequently bismesylated to afford CDs **2α** and **2β** (Scheme 1).[18] Surprisingly, the treatment of **2α** and **2β** with imidazole gave the imidazolium-bridged CDs **3α** and **3β** in 73 and 70% yield, respectively, instead of the corresponding bisimidazoles. When benzimidazole was used, CD **2α** was converted into the azolium-bridged CD **4**. Compound **3α** was deprotected with $Pd(OH)_2$ under an atmosphere of hydrogen to afford the imidazolium-functionalized unprotected CD **5** in 91% yield. Imidazolium compounds **3α**, **3β**, and **4** were treated with Ag_2O to prepare the silver–NHC complexes **7α·AgCl**, **7β·AgCl**, and **8·AgCl**, respectively, in 90, 80, and 88% yield. The unprotected silver–NHC–CD complex **6·AgCl** was obtained in 75% yield through the peracetylation of CD **5**, followed by Ag_2O-mediated carbene formation and controlled deprotection with potassium carbonate in a water/methanol mixture. Not only silver but also copper and gold atoms were complexed with the NHC. The copper complex **7α·CuCl** was generated either by direct treatment of the imidazolium salt **3α** with Cu_2O in 80% yield or through transmetalation of the silver complex **7α·AgCl** with CuCl to give **7α·CuCl** in quantitative yield. This latter strategy was also used to synthesize the gold complexes **7α·AuCl** and **7β·AuCl** from **7α·AgCl** and **7β·AgCl** in 67 and 46% yield, respectively, by treatment with AuCl.

The position of the metal atom inside the cavity was demonstrated by the use of NMR spectroscopy. First, we assigned all proton signals for the imidazolium derivatives and complexes (see the Supporting Information, SI1). A NOESY experiment on the imidazolium compound **3α** showed cross-correlations between the acidic imidazolium hydrogen atom and a pair of hydrogen atoms H-5^{A,D} inside the cavity. Additional cross-correlations between the ethylenic hydrogen atoms of the imidazolium group and the hydrogen atoms H-6^{A,D} on the edge of the cavity fully support the orientation of the carbene precursor toward the center of the cavity (Figure 2; see also the Supporting Information, SI2). These correlations indicate a partial inclusion of the imidazolium ring inside the cavity. The position of the imidazolium ring offers a unique inner coordination site, as further demonstrated by the metal complexes.

A NOESY experiment performed on the copper complex **7α·CuCl** showed the same cross-correlations between the ethylenic hydrogen atoms of the imidazole ring and the outer H-6^{A,D} and H-6^{B,E} hydrogen atoms and thus indicated that the NHC preserves the orientation of the imidazolium ring, with the carbene located within the cavity (Figure 2; see also the Supporting Information, SI3). These correlations were further confirmed by a simple 3D model of **7α·CuCl** (Figure 2), which was in full agreement with the NMR spectroscopic observations.[19] Furthermore, when the ^{1}H NMR spectrum of the imidazolium compound **3α** was compared with that of the complex **7α·CuCl**, an impressive downfield shift of the signals for the hydrogen atoms H-5^{A,D} and H-3^{C,F} was observed ($\delta(\text{H-}5^{A,D})_{7\alpha\cdot\text{CuCl}}-\delta(\text{H-}5^{A,D})_{3\alpha}=1.2$ ppm; $\delta(\text{H-}3^{C,F})_{7\alpha\cdot\text{CuCl}}-\delta(\text{H-}3^{C,F})_{3\alpha}=1.3$ ppm; Figure 3). This deshielding effect exists whatever the metal atom, with varying intensities, and clearly indicates an effect of the complex on the hydrogen atoms



Scheme 1. Synthesis of NHC-capped CDs. Bn = benzyl, Ms = methanesulfonyl (mesyl).

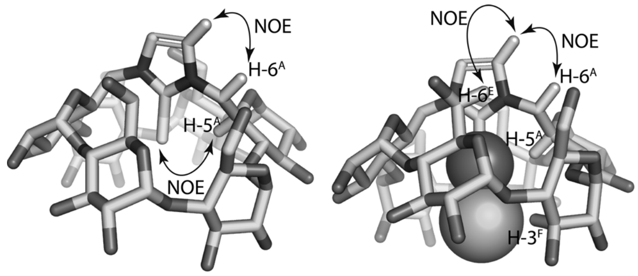


Figure 2. Schematic view of the proposed model. The observed NOE cross peaks are indicated, as well as the deshielded hydrogen atoms ($H\text{-}3^{C,F}$ and $H\text{-}5^{A,D}$) of the imidazolium-bridged cyclodextrin **3 α** (left) and the NHC–CuCl complex **7 α·CuCl** (right). Protecting groups as well as noninteracting hydrogen atoms are omitted for clarity.

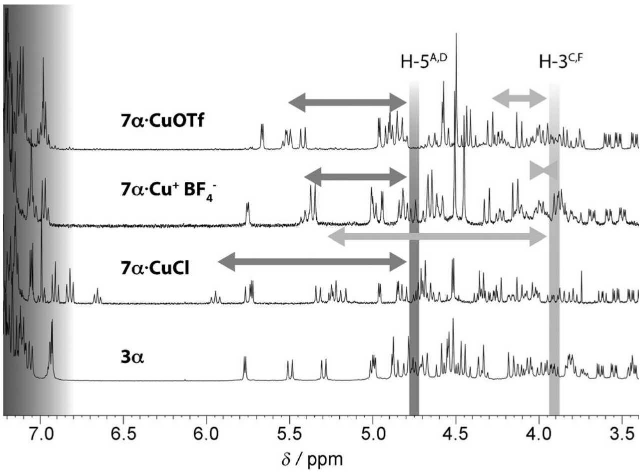


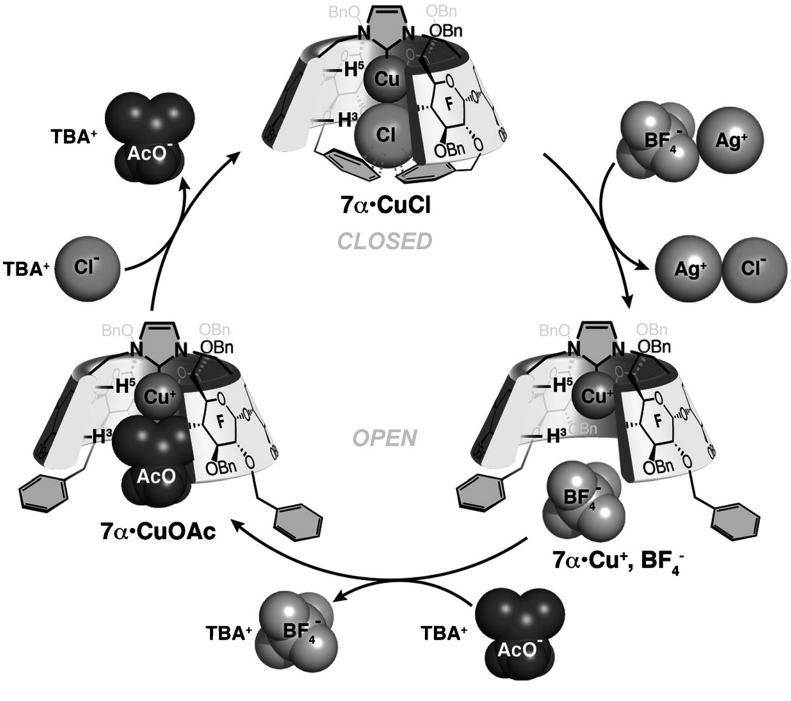
Figure 3. ^{1}H NMR spectra ([D$_6$]acetone, 400 MHz) of the imidazolium derivative **3 α** and the copper complexes **7 α·CuCl**, **7 α·Cu$^+$ BF$_4$$^-$**, and **7 α·CuOTf**. Arrows indicate the chemical-shift differences, $\Delta\delta$, between hydrogen atoms in **3 α** and the corresponding hydrogen atoms in the **7 α·CuX** complexes (the arrows are light gray for $H\text{-}3^{C,F}$ and in dark gray for $H\text{-}5^{A,D}$).

that point toward the inside of the cavity (see the Supporting Information, SI4). In a further experiment, we introduced a protonated ligand into the complex to gain insight on its position inside the cavity. Thus, the chloride atom in **7 α·CuCl** was replaced with a cyclopentadienyl (Cp) anion by the simple addition of NaCp. The hydrogen atoms of the Cp ligand appeared as a singlet, which cross-correlated with the signals of the H-3 and H-5 hydrogen atoms characteristic of the internal part of the CD (see the Supporting Information, SI5). On the basis of this concordant evidence, we concluded that the metal atom was encapsulated inside the cavity of the NHC-capped CDs. Similar observations for the silver/gold complexes **7 α·AgCl/AuCl**, as well as for the NHC-capped β-CD silver/gold complexes **7 β·AgCl/AuCl** and the benzimidazole derivative **8·AgCl**, confirmed the position of the metal inside the cavity in all these cases. In the complexes derived from β-CD, such as **7 β·AgCl**, the asymmetry induced by capping with the NHC translates into differentiation of the deshielded hydrogen atoms in the presence of the metal: $\delta(H\text{-}5^A) = 5.54$ ppm, $\delta(H\text{-}5^D) = 4.44$ ppm, and $\delta(H\text{-}3^C) = 4.60$ ppm, $\delta(H\text{-}3^B) = 4.51$ ppm.

Molecular modeling in conjunction with NMR spectroscopic experiments on **7 α·MX** showed that the metal is buried deep inside the cavity and aligned with $H\text{-}5^{A,D}$, whereas the hydrogen atoms $H\text{-}3^{C,F}$ point toward the counterion. We also observed that the CD torus is slightly distorted by the presence of the capping NHC,[20] which induces a differentiation of the distances between the H-5 atoms and the metal, $d(H\text{-}5^{A,D}–M) < d(H\text{-}5^{B,E}–M) < d(H\text{-}5^{C,F}–M)$, and between the H-3 atoms and the counterion, $d(H3^{C,F}–Cl) < d(H3^{B,E}–Cl) < d(H^{A,D}–Cl)$. Indeed, the $H\text{-}5^{A,D}$ chemical shift is strongly affected by the introduction of the metal ion ($\delta(H\text{-}5^{A,D})_{\mathbf{7\alpha\cdot MCl}} - \delta(H\text{-}5^{A,D})_{\mathbf{3\alpha}} > +1$ ppm; M = Ag, Cu, Au), but also slightly affected by the nature of the counterion ($X^- = Cl^-, Br^-, I^-, AcO^-, BzO^-, TfO^-, BF_4{}^-, SbF_6{}^-$; Bz = benzoyl, Tf = trifluoromethanesulfonyl; see the Supporting Information, SI6). This effect relates to the electron density of the metal: the more electron-rich the metal is, the more deshielded the $H\text{-}5^{A,D}$ hydrogen atoms are (degree of deshielding introduced by the counterion: halogen ligands ≥ carboxylate ligands > free ions). Variation of the NHC structure (imidazole versus benzimidazole) also induces a change in the chemical shift of this pair of hydrogen atoms (the signal for **8·AgCl** is shifted 0.4 ppm downfield relative to the corresponding signal for **7 α·AgCl**). It is therefore logical to attribute this shift to a C–H···M interaction,[21] which indicates that the metal is buried right in the middle of the cavity. This C–H···M interaction was not described for previously reported CD-based metallocavitands, in which a C–H···X interaction was invoked to explain the deshielding of the H-5 hydrogen atoms. In our case, this C–H···X interaction accounts for the deshielding of the $H\text{-}3^{C,F}$ hydrogen atoms, as clearly evidenced by ligand-dependent chemical-shift variations: halogens (Cl, Br, and I) induce a strong deshielding of $H\text{-}3^{C,F}$, which decreases when carboxylates/sulfonates (AcO^-, BzO^-, or TfO^-) or free counterions ($BF_4{}^-$, $SbF_6{}^-$) are used (Figure 3; $\delta(H\text{-}3C,F)_{\mathbf{7\alpha\cdot CuCl}} - \delta(H\text{-}3C,F)_{\mathbf{3\alpha}} = 1.3$ ppm, $\delta(H\text{-}3C,F)_{\mathbf{7\alpha\cdot CuOTf}} - \delta(H\text{-}3C,F)_{\mathbf{3\alpha}} = 0.4$ ppm, $\delta(H\text{-}3C,F)_{\mathbf{7\alpha\cdot CuOTf}} - \delta(H\text{-}3C,F)_{\mathbf{3\alpha}} < 0.1$ ppm; see also the Supporting Information, SI6). Hence, in our system, the metal is aligned with the H-5 atoms: at a level below that occupied in previously described metal-capped CDs. This unique structure of the complexes gives rise to an unusual C–H···M interaction that is unprecedented in metallocavitands.

An additional unusual feature of the NMR spectra of these complexes is the clear upfield shift observed for two triplets in the aromatic region of the ^{1}H NMR spectrum of the perbenzylated complex **7 α·CuCl** (Figure 3). Upon the complete assignment of the NMR spectrum, these signals were eventually attributed to the hydrogen atoms at the *para* and *meta* positions of the benzyl groups linked to the $O\text{-}2^{C,F}$ atoms (see the Supporting Information, SI7). The shielding effect was found to endure when the chlorine atom was exchanged for bromine or iodine, but not to persist when a triflate or $BF_4{}^-$ ion replaced the halogen (Figure 3; see also the Supporting Information, SI6). This shielding effect is symptomatic of a halogen–π interaction[22] and is therefore absent when a carboxylate ligand replaces the halogen. Furthermore, a NOESY experiment on **7α·AgOAc** revealed the absence of a NOE contact between CH_3COO and the aryl hydrogen atoms on the benzyl groups linked to O-2^{C,F} This result demonstrates that these hydrogen atoms are far away from each other, and that these aromatic rings are not in the vicinity of the CD entrance (see the Supporting Information, SI8).

Thus, in the metal–halogen complexes, the benzyl groups define an intramolecular second coordination sphere, which closes the entrance of the cavity at its wider secondary rim; this cavity entrance is opened by the replacement of the halogen with a carboxylate ligand. Therefore, the system should switch from one state to the other through the abstraction or introduction of the halide. Indeed, when we added AgBF$_4$ to the closed-door complex **7α·CuCl**, AgCl precipitated, and the open-door **7α·Cu$^+$ BF$_4^-$** salt was formed. The addition of tetrabutylammonium acetate (TBAOAc) to **7α·Cu$^+$ BF$_4^-$** led to the formation of a new (open-door) species identified as **7α·CuOAc**, which could be converted back into the closed-door complex **7α·CuCl** by the addition of tetrabutylammonium chloride (TBACl) (Scheme 2; see also the Supporting Information). The chloride ligand has to be abstracted prior to ligand exchange: upon the addition of TBAOAc to **7α·CuCl**, nothing happened, but as soon as AgBF$_4$ was added to the solution, **7α·CuOAc** and AgCl were formed. In the water-soluble unprotected derivative **6α·AgCl**, only the H-5^{A,D} atoms appeared to be deshielded. This observation indicates that when the cavity is fully opened, the ligand undergoes rapid exchange with the competing solvent on the NMR timescale. Together, these characteristics show that the supplementary halogen–π interaction (and not only the steric crowding around the metal center) lends additional stability to the perbenzylated complex.



Scheme 2. Opening/closing of the cavity through ligand exchange. TBA$^+$ = tetrabutylammonium.

In metalloproteins, steric shielding of the metal induces particular electrochemical properties, including some degree of isolation from an electrode surface, but with retained reactivity and a high degree of selectivity. The burying of the metal center has also been thoroughly explored in the case of NHCs as ligands, and the percent buried volume (% V_{Bur}) has been defined as a measure of the contribution of the ligand to the steric bulk around the complexed metal.[23] We evaluated the percent buried volume[24] of our simplified model of **7α** and obtained a % V_{Bur} value of 58.5 %, which is, to the best of our knowledge, the highest value found for a monodentate NHC.[25–27] This high value for our NHC-capped CD raises the question of the limit of % V_{Bur} above which no reaction and/or no electron transfer can occur. Furthermore, as mentioned above, the electrochemical properties of metal centers included in CDs have been studied, and the general belief is that the included metal does not transfer electrons; a metal-capped CD, however, does transfer electrons.[18]

We were keen to study this phenomenon with our unique system, in which the metal is in the middle of the cavity, and compared the electrochemical properties of the classical carbene complex chloro[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]copper(I) (IPr·CuCl) with those of our NHC-capped CD **7α·CuCl** (Figure 4). Similarly to its oxidation in dichloromethane, the oxidation of IPr·CuCl occurred in *N*,*N*-dimethylformamide (DMF) at around +1.3 V/SCE (wave O$_1$; SCE = saturated calomel electrode).[28] However, under the same conditions (solvent, scan rate, electrodes,…), no electron transfer could be detected for **7α·CuCl** during the oxidative or reductive scans within the accessible electrochemical window (from +1.8 to −3 V/SCE). The absence of electrochemical signals for **7α·CuCl** cannot be due to a slower diffusion rate than that of IPr·CuCl, since it was shown previously that a copper-capped salen–cyclodextrin complex, in which the metal was placed at the entrance of the cavity, could be reduced and oxidized electrochemically.[18] We can therefore conclude that the cavity in **7α·CuCl** serves to insulate the metal from the electrode.

In our system, the metal is sufficiently insulated by the cavity to prevent electron transfer, and it also displays an exceptionally high % V_{Bur} value. Both of these characteristics are reasons to question the accessibility of the metal as a reactive center. To probe the possibility of catalytic activity, we thus embarked on the study of some benchmark reactions for which the size and/or chirality of the cavity could be an added value. Gold catalysis is currently a field of intense investigation, and NHC–Au complexes possess particularly useful reactivity;[29] we therefore selected well-established diagnostic reactions in this area. We first concentrated on enyne substrate **9**, which has been shown to provide primarily the five-membered-ring products **10a**

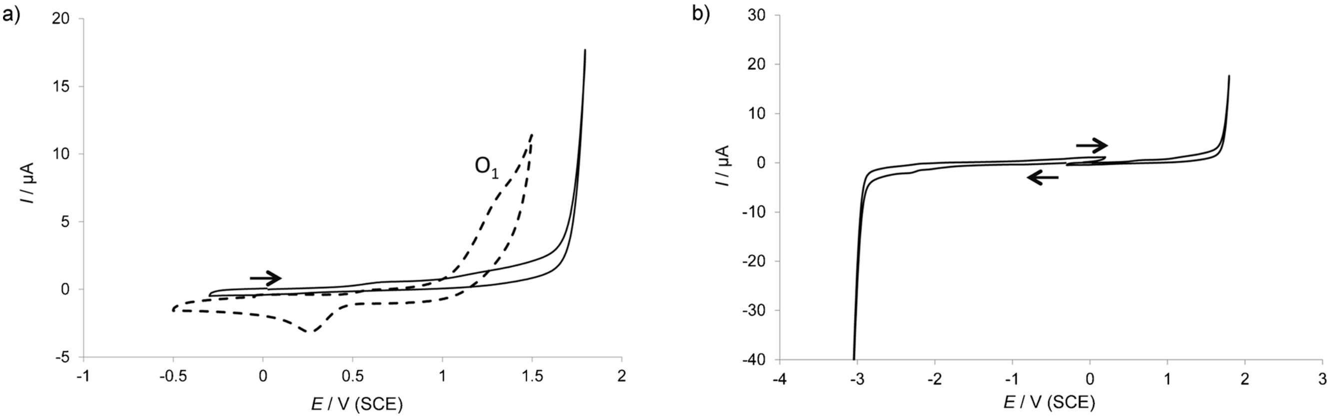
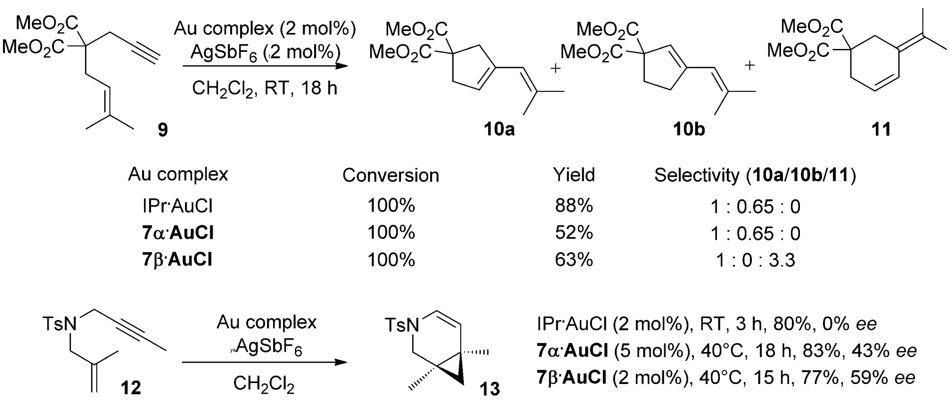


Figure 4. a) Cyclic voltammograms of IPr·CuCl (4 mm; dotted curve) and **7α·CuCl** (4 mm; solid curve) in DMF with TBABF$_4$ (0.1 m) at a glassy carbon electrode (1 mm diameter); scan rate: 0.2 Vs^{-1}. b) Reductive and oxidative scans of **7α·CuCl** (4 mm) under the conditions described for (a).



Au complex	Conversion	Yield	Selectivity (**10a**/**10b**/**11**)
IPr·AuCl	100%	88%	1 : 0.65 : 0
7α·AuCl	100%	52%	1 : 0.65 : 0
7β·AuCl	100%	63%	1 : 0 : 3.3

IPr·AuCl (2 mol%), RT, 3 h, 80%, 0% *ee*
7α·AuCl (5 mol%), 40°C, 18 h, 83%, 43% *ee*
7β·AuCl (2 mol%), 40°C, 15 h, 77%, 59% *ee*

Scheme 3. Gold-catalyzed reactions. Ts = *p*-toluenesulfonyl.

and **10b** upon cyclization.[30] Whereas reactions with complexes IPr·AuCl and **7α·AuCl** obeyed this trend, complex **7β·AuCl** bifurcated the skeletal rearrangement process to give the highest yield of the six-membered-ring product **11** recorded for gold catalysis of this reaction. This result clearly demonstrates the effect of the cavity on the outcome of the reaction. We then examined the possibility of a stereodifferentiating cycloisomerization process from enyne **12**.[31] Good yields of the bicyclic product **13** were observed with the complexes **7α·AuCl** and **7β·AuCl** in reactions featuring quite promising enantioselectivities (the product was formed with 43 and 59% *ee*, respectively). These results illustrate the potential of asymmetric induction by these chiral precatalysts[32] as well as the cavity-dependent selectivity[33] of the complexes (Scheme 3).

In conclusion, we have efficiently synthesized a new family of NHC-capped CDs and their corresponding copper, silver, and gold complexes. NMR spectroscopy and ligand-exchange studies showed that the metal is located inside the cavity, where it induces a strong deshielding effect on a pair of H-5 atoms. The counterion accounts for the deshielding of H-3, and in the case of halogens, for the shielding of aromatic hydrogen atoms. The metal–halogen complexes exhibited a unique combination of C−H···M, C−H···X−M, and π···X−M interactions, which underline the unusual environment of the metal center encapsulated inside the CD torus. Furthermore the halogen–π interaction induces the closing of the cavity by two benzyl groups on the secondary rim; the cavity can, however, be opened through ligand exchange. During this study, we also formally demonstrated that a metal inside a CD cavity was indeed insulated from an electrode surface; this characteristic had only been postulated previously. Finally, encapsulation did not prevent the metal from being reactive. In fact, our NHC-capped CD ligands (ICyDs) promote unique reactivity that is clearly linked to the structure of the cavity.

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Keywords: cavitands · cyclodextrins · electrochemistry · homogeneous catalysis · N-heterocyclic carbenes

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