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Permethylated NHC-capped α- and β-cyclodextrins ($\mathbf{ICyD^{Me}}$)
Regioselective and enantioselective gold-catalysis in pure water

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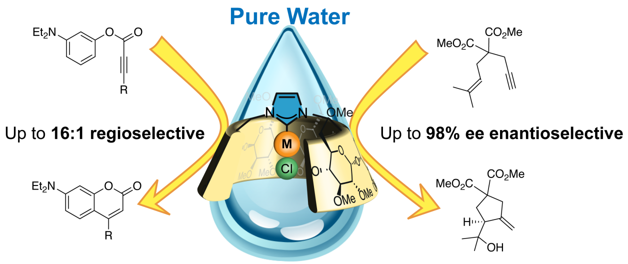


Abstract

A series of water-soluble encapsulated copper(I), silver(I) or gold(I) complexes based on NHC-capped permethylated cyclodextrins ($\mathbf{ICyD^{Me}}$) were developed and used as catalysts in pure water for hydration, lactonization, hydroarylation and cycloisomerization reactions. $\mathbf{ICyD^{Me}}$ ligands gave cavity-based high regioselectivity in hydroarylations, and high enantioselectivities in gold-catalyzed cycloisomerizations reactions giving up to 98% ee in water. These $\mathbf{ICyD^{Me}}$ are therefore useful ligands for selective catalysis in pure water.

Keywords Cyclodextrin, N-heterocyclic carbene, cavity, catalysis, water

Introduction

Encapsulation of metal centers inside molecular cavities is classically viewed as a way to imitate metallo-enzymes.[1] This strategy actually allowed selectivities in chemical reactions resembling those of enzymes: regioselectivity,[2] enantioselectivity,[3] substrate selection[4]… However, only a few reactions are operating in the solvent of enzymes: water.[5] Some time ago, we uncovered a series of *N*-heterocyclic carbene (NHC)-capped cyclodextrins (CDs) which encapsulate metal centers inside the cavity.[6] The structure/properties of these complexes are flexible and can be modulated by changing the nature of the NHC (imidazolyl, benzimidazolyl or triazolyl), the size of the CD macrocycle (α, β or γ-CD), the structure of the embedded metal complex, or the nature of *O*-protecting groups (-OR, R = H, Ac or Bn), these latter affecting metal surroundings and solubility. In organic solvents, we demonstrated that the outcome of some metal-catalyzed reactions was dependent on the nature of the CD (α-, β- or γ-CD) and could be linked to the shape of the cavity. Particularly, benzyl-protected CD–imidazolyl ligands, called **ICyD**, were found to induce CD-dependent enantioselectivity or variation of product distribution in gold-catalyzed cycloisomerizations,[6,7] CD-dependent regioselectivity in copper-catalyzed hydroboration,[8] and chemoselectivity in a hydrosylilation controlled by the cavity size.[9] An obvious development, when using CD scaffolds, is their application in water. Water-soluble CD–NHC–silver complexes were previously obtained by generation of a free hydroxy ligand (non-protected CD) from α-**ICyD**.[6] Another classical way to get water-soluble CDs is to partially or fully methylate the hydroxyl groups. A benzimidazolyl-capped α-CD ligand having full OH protection by methyl groups was recently reported.[10] The catalytic properties of the corresponding gold complex was evaluated in organic solvents. This methylated ligand (α-$\mathbf{BiCyD^{Me}}$) was found to behave similarly to the previously described benzylated one (α-**BiCyD**)[7] in standard gold-catalyzed cycloisomerization reactions.[6,7]

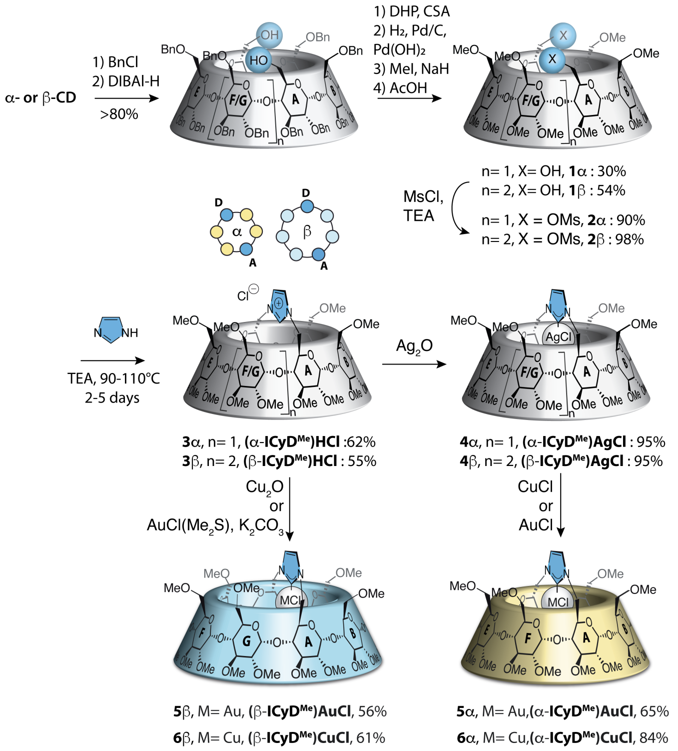
[†] These authors contributed equally to this work.

We present here applications in water of a series of water-soluble (**ICyD^{Me}**)MCl complexes (M = Au, Ag, Cu) derived from α- and β-CD. The preparation and full structural study of **ICyD^{Me}**-based complexes is reported with NMR structural analyses both in water and organic solvents and X-ray structures obtained from crystallization both in water and organic solvents. More importantly, we present our investigations concerning the catalytic applications of encapsulated (**ICyD^{Me}**)MCl complexes in pure water over a variety of reactions: hydrations, lactonizations, hydroarylations and enantioselective cycloisomerizations, with a particular focus on gold-catalyzed reactions.

Results and discussion

Synthesis of water-soluble (ICyD^{Me})MCl complexes

Synthesis of water-soluble α- and **β-ICyD^{Me}** metal complexes started with the classical perbenzylation/double-debenzylation sequence,[11,12] followed by an optimized conversion of the as-obtained perbenzylated diol into the corresponding permethylated one.[13] Hence THP protection, hydrogenolysis, methylation and THP cleavage, yielded diols **1α** and **1β** in 30% and 54% yields over four steps, respectively. Mesylation of both diols proceeded smoothly to give **2α** and **2β** in high yields. The next step was formation of imidazolium derivatives. The reaction conditions previously used for the formation of the perbenzylated **ICyD** azoliums (imidazole 20 equiv, DMF, 120 °C, overnight) were found not operative here as they gave the expected (**α-ICyD^{Me}**)HCl salt **3α** in very low yields together with partial hydrolysis and formylated products. This result was also observed by Armspach in attempts to use these conditions to cap the same CD derivative, but with benzimidazole.[10] However, upon analysis of the secondary products, we attributed this problem to the predominance of a non-expected reaction with DMF and to the large excess of imidazole. Hence, DMF was replaced with toluene and acetonitrile to favor imidazole solubilization; the amount of imidazole was decreased from 20 to 3 equivalents and triethylamine was used as the base. Subsequent heating for 3 days allowed to obtain imidazolium (**α-ICyD^{Me}**)HCl **3α** after ion exchange in 62% yield. The bridging of the β-CD **2β** into (**β-ICyD^{Me}**)HCl **3β** (55% yield) required even longer reaction times probably due to the larger size of the cavity. Both silver complexes (**α-ICyD^{Me}**)AgCl **4α** and (**β-ICyD^{Me}**)AgCl **4β** were obtained quantitatively upon action of Ag_2O on the corresponding imidazolium salts. To get the corresponding copper and gold complexes two distinct routes had to be taken for α-CD and β-CD derivatives. The direct metalation was used to get (**β-ICyD^{Me}**)AuCl **5β** and (**β-ICyD^{Me}**)CuCl **6β**, while transmetalations from silver complexes were required to obtain (**α-ICyD^{Me}**)AuCl **5α** and (**α-ICyD^{Me}**)CuCl **6α**. (Scheme 1)



Scheme 1. Synthesis of (**α-ICyD^{Me}**)MCl and (**β-ICyD^{Me}**)MCl (M=Ag, Cu, Au).

Structure of (ICyD^{Me})MCl complexes.

All (**ICyD^{Me}**)MCl complexes were first characterized by NMR in organic solvents ($CDCl_3$ or CD_3CN). As for previously reported (**ICyD**)MCl complexes, the ^{1}H NMR spectra of all **ICyD^{Me}**-based complexes displayed deshieldings of H-5 and H-3 protons typical of a M-Cl complex confined inside the CD cavity. Owing to the water solubility of the permethylated CDs, NMR spectra in D_2O were also recorded for the silver complexes (**α-ICyD^{Me}**)AgCl **4α** and (**β-ICyD^{Me}**)AgCl **4β**. Interestingly, significant differences with the spectra in organic solvents have been found. For comparison, the ^{1}H NMR spectra of **4α** in $CDCl_3$ and D_2O are displayed on Figure 1. In $CDCl_3$, the most deshielded intra-cavity protons are H-5^{A,D} and H-3^{C,F}, as observed with the benzylated complex (**α-ICyD**)AgCl **4α**, which indicates that the shape of the cavity is probably the same in both cases. However, in D_2O, the order of chemical shifts between H-3s is changed, and H-3^{A,D} becomes more deshielded than H-3^{C,F}. This observation suddenly rises questions, in particular about the shape of the cavity in water, or even on the validity of our assumption concerning the relationship between distance of internal Hs and the metal complex with their deshielding. It therefore became compulsory to obtain a crystal structure of **ICyD**-based metal complexes.

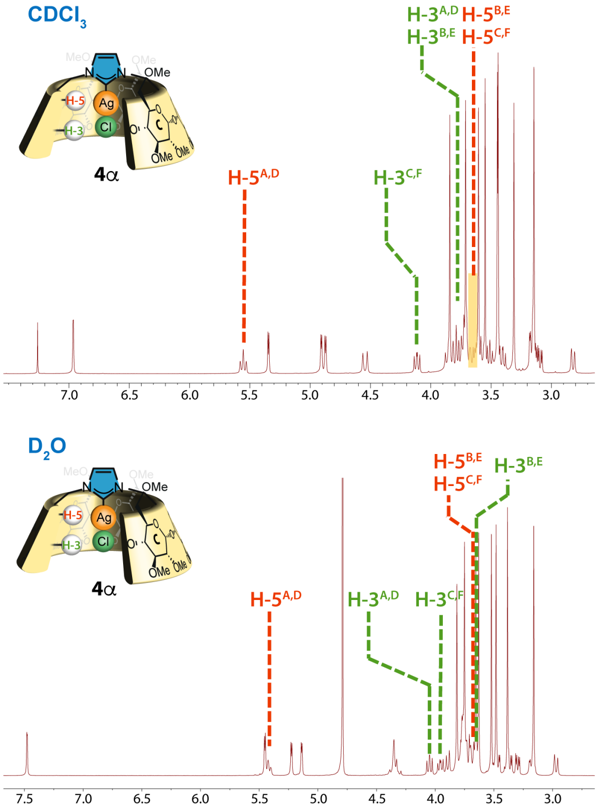


Figure 1. ^{1}H NMR spectra of (**α-ICyD^{Me}**)AgCl (**4α**,400 MHz) in $CDCl_3$ and in D_2O.

Single crystals of (**α-ICyD^{Me}**)AgCl (**4α**) could be obtained through slow diffusion of pentane and cyclohexane into a solution of the complex in $CDCl_3$. Interestingly enough, **4α** also crystallized from deuterated water. Both structures were resolved and are displayed on Figure 2. At first glance, the structures obtained are identical, and confirm the encapsulation of the metal inside the CD torus. However, upon closer examination, striking differences could be detected in particular when examining the H-3…Cl distances. The structure issued from crystallization in organic solvents was symmetrical, as expected, and the distances between H-5s and the metal, and those between the H-3s and the chlorine were in the same order as their chemical shifts as previously hypothesized the closer to the metal or the halogen, the more deshielded.[7] The examination of the structure issued from crystallization in water revealed an asymmetry of the cavity, all distances between H-3s and chlorine are different, a feature which is not apparent from the NMR spectrum. Furthermore, H-3^A and H-

3^{D} are further away from chlorine than H-3^{C} and H-3^{F} on the structure but they are the most deshielded on the NMR spectrum. This contradiction with our previous assumptions needed to be resolved. Upon careful examination of both crystal structures, two molecules of water could be found in the cavity of the CD in each case, even when (**α-ICyD^{Me}**)AgCl (**4α**) was crystalized from organic solvents. Interestingly, these water molecules are not situated exactly at the same place in both structures but they are both close to H-3^{A} and H-3^{D}. In the solid phase these water molecules are in interaction through hydrogen bonding with both the chlorine atom and these H-3s. The presence of water hence nicely explains the geometry and the NMR in which the H-$3^{A,D}$ are deshielded because of their interaction with water molecules in aqueous solution but not in organic solvents (although they are present in the crystal packing).

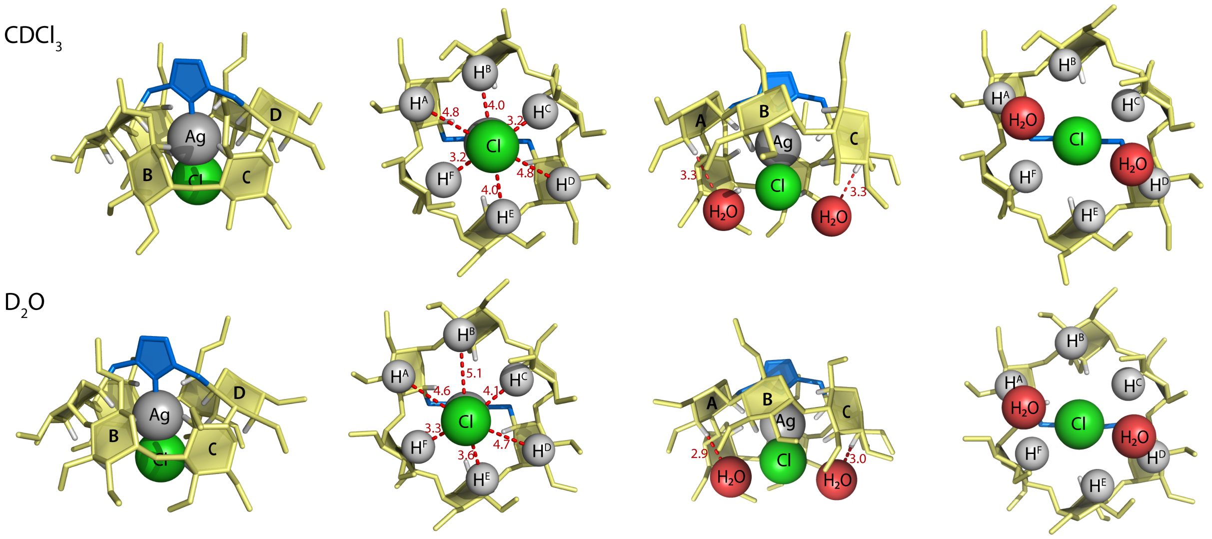


Figure 2. X-ray crystal structure of (**α-ICyD^{Me}**)AgCl **4α** from $CDCl_3$/Pentane/Cyclohexane (A) and from D_2O (B), distances between H-3s and Cl are given in Å and as the average of those found in crystal.

To further support this hypothesis, a temperature-dependent NMR analysis was performed with **4α** in D_2O. Upon heating, a shielding of H-$3^{A,D}$ was observed while H-$3^{C,F}$ chemical shift remained constant (Figure 3), demonstrating that the shielding of H-$3^{A,D}$ is brought by an exchange process, while that of H-$3^{C,F}$ is independent of the temperature and therefore is not brought by a dynamic process. We therefore propose that the water–H-$3^{A,D}$ interaction is present in aqueous solution and that this is responsible for the strong deshielding of this proton.

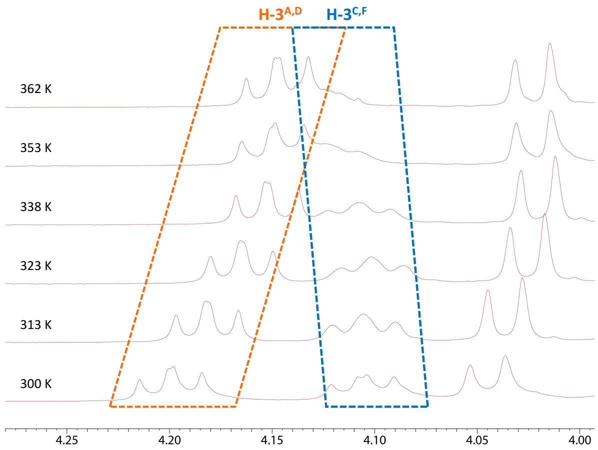


Figure 3. Temperature-dependent ^{1}H NMR of (α-**ICyD^{Me}**)AgCl (**4α**, 600 MHz, D_2O). Comparison of H-$3^{A,D}$ and H-$3^{C,F}$ chemical shifts at different temperatures.

Catalysis in pure water with (ICyD^{Me})MCl complexes

In this study, the catalytic properties of water-soluble (**ICyD^{Me}**)MCl complexes with encapsulated Ag, Cu, or Au, have been investigated in a series of reactions with a particular focus on the use of water as the sole solvent and on gold-catalyzed reactions. Water has been shown to have a particular effect on reactivity and/or selectivity in some reactions. It has also been seen as an alternative reaction medium to reduce the environmental impact of (organic) synthesis,[14] although other factors such as extraction and purification have to be taken into consideration here. More importantly, the development of water-compatible gold-, silver-, or copper-based catalytic systems, is highly interesting for in vivo applications.[15] One of the main limitations for developing catalytic reactions in pure water is the inherently low solubility of most organic materials, including reaction substrates and catalysts. In many studies, an organic co-solvent was added to circumvent these solubility issues. Alternatively, hydrophilic ligands have been developed for catalyst solubilization, and many examples have been reported in copper and gold homogeneous catalysis.[14,16] To the best of our knowledge, this strategy was not particularly explored for silver-based catalysis in water.[14,17] Furthermore, the increasing importance of *N*-heterocyclic carbenes (NHC) as ligands has induced increasing efforts to develop hydrophilic NHCs for metal-based catalysis in aqueous media,[18,19,20,21,22] and medical applications.[23] Ionic salt-tagged NHC ligands have been designed for gold-catalyzed alkyne hydration,[24,25,26,27] cycloisomerization reactions,[26,28,29,30] and copper-catalyzed azide-alkyne cycloadditions (CuAAC).[31,32] Although, water-soluble silver–NHCs have been described since 2004 as antibacterial agents,[33] they have mainly been used as carbene transfer agents,[24,34] and their application in homogeneous catalysis in water remains underexplored.[35] In addition, examples of encapsulated Cu, Ag or Au-based catalytic systems operating in water are scarce or nonexistent. To the best of our knowledge, only two systems with encapsulated gold atoms operating in water are reported.[36,37] A gold-catalyzed hydroalkoxylation reaction with a phosphane-gold(I) complex confined in a (supra)molecular cage was described in a 6:4 D_2O/MeOH mixture.[38] One example using a NHC-Au complex was reported with a supramolecular capsule. This system was used for alkyne hydration in benzene-*d₆* with small amounts of H_2O.[39,40] Encapsulated sulfonated copper phthalocyanine complexes in a protein cavity (BSA) were reported for Diels-Alder reactions in aqueous medium.[41] Recently, a bio-inspired imidazole-functionalized copper cage complex was developed for benzylic alcohol oxidation in water.[42]

Hydration reactions:

In a first series of experiments, the potential of (α-**ICyD^{Me}**)MCl and (**β-ICyD^{Me}**)MCl complexes (M = Au, Ag, Cu) was evaluated in the classical alkyne hydration reaction with different alkynes (**7**-**10**) (Scheme 2). All reactions were first tested using D_2O as the sole solvent. The reactions were run at 20 or 50 °C in NMR tubes and monitored by ^1H NMR. Yields were directly determined by comparison with the internal reference. The results are summarized in Table 1. At 20 °C, both gold complexes (α-**ICyD^{Me}**)AuCl **5α** and (**β-ICyD^{Me}**)AuCl **5β** (0.5 mol%) were found to allow efficient hydration[43] of water-soluble substrate 5-hexyn-1-ol **7** without pre-activation of the catalyst by a silver salt,[27,44] to give the corresponding bis-deuterated methyl ketone **11** in 92-99% yields (Table 1, entries 1-2). The β-CD-derived catalyst **5β** appeared more active than the α-CD-based **5α**, leading to complete conversion and quantitative NMR yield after 14 h. This result is similar to that reported for the hydration of **7** in neat water using ammonium-tagged water-soluble NHC-gold complexes at the same catalyst loading (0.5 mol%).[27] The alkyne **8** reacted slowly at 20 °C with both **5α** and **5β** as gold catalysts, to give **12** in 8-10% yield after 24 h under similar conditions (data not shown). Increasing the temperature to 50 °C was necessary to obtain the bis-deuterated ketone **12** in 88-95% yields (Table 1, entries 3-4). As observed with alkyne **7**, the hydration of **8** is faster when catalyzed by (**β-ICyD^{Me}**)AuCl **5β**, that leads to a complete conversion after 24 h. The limitation of using deuterated water as the sole solvent appeared with the more lipophilic alkyne substrates **9** and **10**. In contrast to **7**, the terminal alkyne **9** was found to react hardly in neat water, but gave good yields by using deuterated methanol as co-solvent to give bis-deuterated ketone **13** in 85-99% NMR yields (Table 1, entries 7-8).[45] Here also, the larger β-**ICyD^{Me}** ligand afforded better yields, probably due to easier accessibility of the substrate to the metal.[46] This trend was clearly confirmed with internal alkyne **10**. Hence, under standard conditions (50 °C), **10** did not react with α-CD-based catalyst **5α**, while (β-**ICyD^{Me}**)AuCl **5β** allowed its hydration, to give ketone **14** in 26% yield, demonstrating some size selection of the substrate by the **ICyD**-based catalysts albeit not in water but in methanol (Table 1, entries 9-10). With terminal alkynes and Au catalysts, Markovnikov addition of water is usually observed to give the methyl ketones.[44] However, an encapsulated NHC–Au complexes was previously shown by Reek an co-workers to give detectable amounts (4%) of the aldehyde regioisomer in the hydration of 4-phenyl butyne **9** in a water-saturated benzene-*d₆* solution.[47] To compare with this result, the regioselectivity of the hydration of **9** catalyzed by encapsulated (**ICyD^{Me}**)AuCl complexes was studied in H_2O. Over prolonged heating at 50 °C for 7 days, both α and β-CD-derived (**ICyD^{Me}**)AuCl complexes were found to induce non-negligible formation of aldehyde (up to 3 %), along with 20-27% of the expected methyl ketone **12** (see Figure and Table S1 in the supporting information). This result is comparable to that previously observed by Reek and co-workers.[39]

Very few examples of silver-based catalytic systems have been reported for hydration reactions in water.[17] Silver nanoparticles were used for the selective hydration of nitriles,[48] and a silver salt of heteropolytungstate was reported for hydration of alkynes.[49] Both systems involve heterogeneous catalysis. Silver nitrate ($AgNO_3$) in water was shown to give slow hydration of phenylacetylene at 100 °C (15% conversion).[49] Therefore, the catalytic activity of (**ICyD^{Me}**)AgCl complexes was investigated in the hydration reaction of alkynes **7**-**10** in water (Table 1, entries 11-15). In contrast to the corresponding gold complexes, both (**α-ICyD^{Me}**)AgCl **4α** and (**β-ICyD^{Me}**)AgCl **4β** were found to be inactive for the hydration of water-soluble alkyne **7** at 20 °C (data not shown). However, at 50 °C, **4α** (0.5 mol%) efficiently induced the formation of the expected bis-deuterated methyl ketone **11** which was obtained in 92% NMR yield (Table 1, entry 11). Here also, a significant difference with gold complexes was observed, since **4β** was found ineffective in the same reaction, leading to no conversion (Table 1, entry 12). To investigate why (β-**ICyD^{Me}**)AgCl was less effective, we followed the reaction by NMR (with **7**) and showed that in water at 50 °C the β-CD-based silver catalyst **4β** was decomposing. In contrast, **4α** is stable under these conditions and allows the reaction to take place, hence demonstrating the high stabilizing effect of the CD cavity in this latter case. (α-**ICyD^{Me}**)AgCl **4α** also catalyzes the conversion of **8** into the methyl ketone **12** (49% yield, Table 1, entry 13). As for gold complexes, the reaction is difficult with lipophilic alkynes, and both **4α** and **4β** were found to be inefficient for the transformation of **9** and **10**, even in the presence of methanol (Table 1, entries 14-15). Finally, (α-**ICyD^{Me}**)CuCl **6α** and (β-**ICyD^{Me}**)CuCl **6β** did not allow the hydration of the studied alkynes under the same conditions (Table 1, entries 16-18).

Scheme 2. Hydration reaction of alkynes **7**-**10** with D_2O catalyzed by (**ICyD^{Me}**)MCl complexes (M = Au, Ag, Cu). (**A**) Terminal alkynes, (**B**) internal alkyne. Methanol-*d$_4$* was used as co-solvent in some reactions.

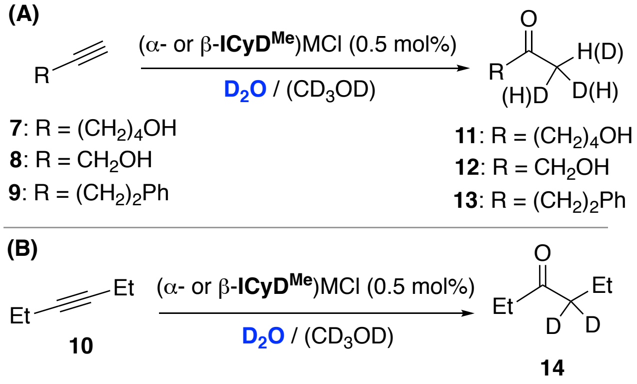


Table 1. Hydration of alkynes **7**-**10** in D_2O catalyzed by (**ICyD^{Me}**)MCl complexes.

Entry	alkyne	Ligand	M	Complex	co-solvent	*T* (°C)	*Time* (h)	*Convn* (%)[b]	*Yield* (%)[c]
1	**7**	α-**ICyD^{Me}**	Au	**5α**	-	R.T.	22	>99	92
2	**7**	β-**ICyD^{Me}**	Au	**5β**	-	R.T.	14	>99	99
3	**8**	α-**ICyD^{Me}**	Au	**5α**	-	50	120	>99	88
4	**8**	β-**ICyD^{Me}**	Au	**5β**	-	50	24	>99	95
5	**9**	α-**ICyD^{Me}**	Au	**5α**	-	50	48	8	<1
6	**9**	β-**ICyD^{Me}**	Au	**5β**	-	50	48	17	<1
7	**9**	α-**ICyD^{Me}**	Au	**5α**	CD_3OD[a]	50	120	95	85
8	**9**	β-**ICyD^{Me}**	Au	**5β**	CD_3OD[a]	50	70	>99	99
9	**10**	α-**ICyD^{Me}**	Au	**5α**	CD_3OD[a]	50	96	<1	<1
10	**10**	β-**ICyD^{Me}**	Au	**5β**	CD_3OD[a]	50	90	92	27
11	**7**	α-**ICyD^{Me}**	Ag	**4α**	-	50	41	>99	92
12	**7**	β-**ICyD^{Me}**	Ag	**4β**	-	50	14	<1 [d]	<1
13	**8**	α-**ICyD^{Me}**	Ag	**4α**	-	50	120	60	49
14	**9**	α-**ICyD^{Me}**	Ag	**4α**	-	50	48	<1	<1
15	**9/10**	α /β-**ICyD^{Me}**	Ag	**4α/4β**	CD_3OD[a]	50	48-72	<1	<1
16	**7**	α-**ICyD^{Me}**	Cu	**6α**	-	50	96	<1	<1
17	**7**	β-**ICyD^{Me}**	Cu	**6β**	-	50	12	<1[d]	<1
18	**9/10**	α /β-**ICyD^{Me}**	Cu	**6α/6β**	CD_3OD[a]	50	28	<1[d]	<1

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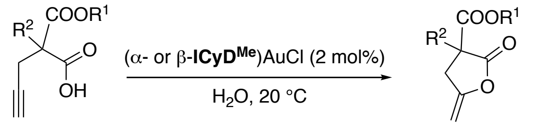
[a] Ratio D_2O/CD_3OD = 1:10; [b] Conversion of the alkyne determined by ^{1}H NMR by comparison of the amount of residual alkyne with the internal reference (butadiene sulfone); [c] NMR yield of methylketone determined by ^{1}H NMR by comparison with the internal reference; [d] A precipitate was observed for β-**ICyD^{Me}**-based catalysts.

Gold-catalyzed lactonization reactions in pure water:

Another classical gold-catalyzed reaction is the intramolecular addition of carboxylic acids to alkynes,[50] which has been developed in aqueous media,[51] and with water-soluble NHC ligands.[26,28,30,52] Therefore, the catalytic activity of both **5α** and **5β** was tested in the lactonization of three γ-alkynoic acids (**15**-**17**), in pure water (Scheme 3). At 20 °C, both catalysts allowed formation of the corresponding lactones **18**-**20** with no detectable formation of the methyl ketone resulting from competitive hydration reaction (Table 2, entries 1-6).[26] The reaction is relatively slow with variable yields ranging from 33 to 85% after 14 or 36 h. The β-CD derivative **5β** gave higher yields in shorter reaction times than the α-CD **5α** with alkynes **15** (14h vs 36 h), **16** (55% vs 33%) and **17** (85% vs 76%) probably due to its larger cavity and therefore easier access to the metal (entries 2, 4 and 6). By comparison, the lactonization of 4-pentynoic acid in neat water was reported to give complete conversion within 1 h with ammonium-tagged NHC-gold(I) complexes under similar conditions (2.5 mol% of catalyst, r.t.).[30] This shows (although the substrates are not identical) that encapsulation of the reactive gold center in the CD cavity in **5α** and **5β** likely leads to lower reaction rates. Importantly, aqueous solutions of both **5α** and **5β** catalysts could be reused in a second cyclization reaction after extraction of organic compounds, to give lactone **19** in comparable yields (25 and 55%) from alkyne **16** (Table 2, entries 7-8), suggesting in particular, that the more accessible β-CD-based catalyst **5β** remains stable in the (acidic) aqueous medium of the reaction.[53] All the reactions presented in Table 2 were conducted without silver(I) salts.

Scheme 3. Lactonization reaction of γ-alkynoic acids **15**-**17** catalyzed by (**ICyD^{Me}**)AuCl complexes.



15: R^1 = H, R^2 = $CH_2C{\equiv}CH$
16: R^1 = Me, R^2 = $CH_2C{\equiv}CH$
17: R^1 = Me, R^2 = $CH_2CH{=}CH_2$

18: R^1 = H, R^2 = $CH_2C{\equiv}CH$
19: R^1 = Me, R^2 = $CH_2C{\equiv}CH$
20: R^1 = Me, R^2 = $CH_2CH{=}CH_2$

Table 2. Lactonization reactions catalyzed by (**ICyD^{Me}**)AuCl complexes in pure water.

Entry	Substrate	Ligand	Complex	Time (h)	Yield (%)[a]
1	**15**	α-**ICyD^{Me}**	**5α**	36	58
2	**15**	β-**ICyD^{Me}**	**5β**	14	58
3	**16**	α-**ICyD^{Me}**	**5α**	36	33
4	**16**	β-**ICyD^{Me}**	**5β**	14	55
5	**17**	α-**ICyD^{Me}**	**5α**	14	76
6	**17**	β-**ICyD^{Me}**	**5β**	14	85
7[b]	**16**	α-**ICyD^{Me}**	**5α**	36	25
8[b]	**16**	β-**ICyD^{Me}**	**5β**	14	55

[a] Isolated yields; [b] Reactions performed after recycling of (α-**ICyD^{Me}**)AuCl and (β-**ICyD^{Me}**)AuCl (second run).

Regioselective hydroarylation in pure water:

Recently, Mascareñas[15] reported a Gold-catalyzed hydroarylation[54,55] in pure water, and even *in cellulo*, using water-soluble phosphine with Au^I and no silver salts. In his study, aryl **21** was used and gave 12% yield of product **22** in pure water; this yield was improved up to 99% using acetonitrile as co-solvent. We therefore tried this reaction with **5α** and **5β** in pure water and could observe an increase in yield when using the larger β-CD derivative (31%). We also used a compound with a smaller substituent on the alkyne, **23**, and observed better yields of **24** with both our catalysts probably due to both a better water-solubility of the substrate and an easier reaction with the catalyst. (Scheme 4, Table 3)

Scheme 4. Hydroarylation of compounds **21** and **23** catalyzed by (**ICyD^{Me}**)AuCl complexes.

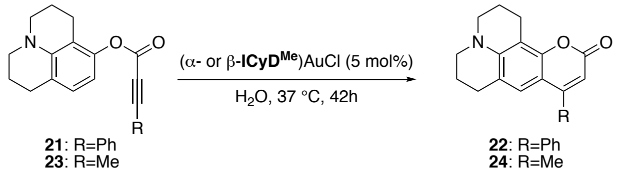


Table 3. Hydroarylation of compounds **18** and **20** catalyzed by (**ICyD^{Me}**)AuCl complexes in pure water.

Entry	Substrate	R	Ligand	Complex	Yield (%)[a]
1	**21**	Ph	α-**ICyD^{Me}**	**5α**	14
2	**21**	Ph	β-**ICyD^{Me}**	**5β**	31
3	**23**	Me	α-**ICyD^{Me}**	**5α**	19
4	**23**	Me	β-**ICyD^{Me}**	**5β**	52

[a] Isolated yields.

Substrate **21** was initially designed by Mascareñas to avoid regioselectivity problems in the hydroarylation reaction.[15] Indeed, the use of compound **25c** with no substituents on both *ortho*-positions to the ester, was reported by the same group to give a mixture of both **26c** and **27c** (ratio from 1.5:1 to 10:1 depending on the gold catalyst used).[15] We therefore probed our catalysts in this reaction with a series of aryl **25a-c** and observed a good regioselectivity in all cases in favor of compounds **26a-c**. The best regioselectivity (16:1) was obtained with **25b** and β-**ICyD^{Me}** as ligand (entry 4). Encapsulation of Au^{I} inside the ICyD^{Me} ligands therefore promotes regioselectivity in this hydroarylation reaction in pure water without silver salts. (Scheme 5, Table 4)

Scheme 5. Hydroarylation of compounds **25a-c** catalyzed by (**ICyD^{Me}**)AuCl complexes.

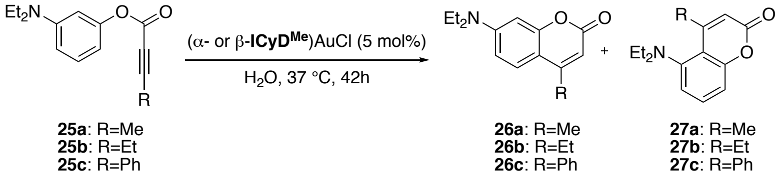


Table 4. Hydroarylation of compounds **25a**-**c** catalyzed by (**ICyD^{Me}**)AuCl complexes in pure water.

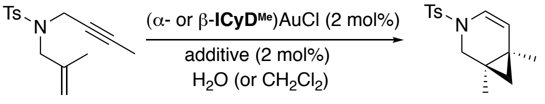
Entry	Substrate	Ligand	Complex	Yield (%)[a]		**26:27**
				26x	**27x**	ratio
1	**25a**	α-**ICyD^{Me}**	**5α**	85	12	7:1
2	**25a**	β-**ICyD^{Me}**	**5β**	82	12	7:1
3	**25b**	α-**ICyD^{Me}**	**5α**	80	14	6:1
4	**25b**	β-**ICyD^{Me}**	**5β**	80	5	16:1
5	**25c**	α-**ICyD^{Me}**	**5α**	53	7	8:1
6	**25c**	β-**ICyD^{Me}**	**5β**	77	9	9:1

[a] Isolated yields.

Enantioselective gold-catalyzed cycloisomerizations in pure water:

Examples of asymmetric gold catalysis in water or in the presence of water, involving chiral ligands, remain scarce.[56,57,58,59,60] Michelet and co-workers reported enantioselective hydroxy-cyclizations of 1,6-enynes in dioxane/H_2O (6:1).[57,58] An enantioselectivity up to 72% was reached with chiral phosphane ligands in combination with silver salts. Chiral phosphoramidites (with $AgBF_4$) were reported by Toste and co-workers to give 96% *ee* in allene-ene hydroxycyclization in water.[59] An enantioselective intramolecular cyclization of allenic acids in aqueous nanomicelles was reported by Lipshutz and co-workers to give up to 96% *ee* with chiral biaryl phosphane ligands.[60] To the best of our knowledge, enantioselective gold-catalyzed reactions in pure water with chiral hydrosoluble NHC ligands have not been reported. The potential of both (α-**ICyD^{Me}**)AuCl **5α** and (β-**ICyD^{Me}**)AuCl **5β** to induce enantioselectivity in water was first studied in the cycloisomerization of *N*-tethered enyne **28** (Scheme 6 and Table 5).[61] In contrast to the previous hydration and lactonization reactions, the reaction was found not to proceed in the absence of silver salts, regardless of the complex used (Table 5, entry 1). In the presence of $AgSbF_6$, however, the cyclized product **29** was obtained in 13-25% yields after 16 h (entries 2 and 3). A higher temperature of 50 °C was required with catalyst **5α** likely due to the superior steric constraint imposed by the α-CD cavity. Although the yields are low, satisfactory enantioselectivities of 60 and 81% were obtained **5α** and **5β**, respectively (Table 3, entries 2 and 3). The highest *ee* for **29** was obtained at 20 °C with the larger β-CD-based catalyst **5β**. We previously reported the enantioselective cycloisomerization of the same enyne **28** in an organic solvent (CH_2Cl_2), with the perbenzylated analogues of **ICyD^{Me}** ligands.[7] Interestingly, both water-soluble α-**ICyD^{Me}** and β-**ICyD^{Me}** ligands in water were found to give significantly higher enantioselectivity than the previous standard α-**ICyD** and β-**ICyD** ligands in organic medium (compare entries 2/4 and 3/5) (Scheme 6, Table 5)

Scheme 6. Enantioselective enyne cycloisomerization of **28**.



28 (+)-(*R*,*R*)-**29**

Table 5. Enantioselective enyne cycloisomerization of **28** in pure water or CH_2Cl_2.

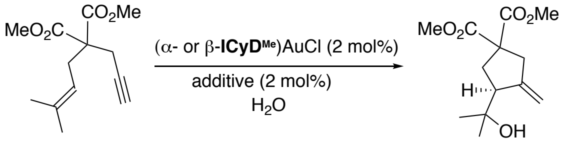
Entry	Ligand	Complex	Solvent	Additive	*T* (°C)	Yield (%)[a]	*ee* (%)[b]
1	α /β-**ICyD^{Me}**	**5α/5β**	H_2O	-	50	<1	-
2	α-**ICyD^{Me}**	**5α**	H_2O	$AgSbF_6$	50	13	60
3	β-**ICyD^{Me}**	**5β**	H_2O	$AgSbF_6$	20	25	81
4[c]	α-**ICyD**	**5α**	CH_2Cl_2	$AgSbF_6$	40	83	43
5[c]	β-**ICyD**	**5β**	CH_2Cl_2	$AgSbF_6$	20	77	59

[a] Isolated yields after 16 h of reaction; [b] Enantiomeric excess determined by chiral HPLC; [c] Previous results with benzyl-protected CD ligands (ICyD) see ref. 7.

The role of silver salts in this particular reaction remains unclear. To the best of our knowledge, enyne cycloisomerization reactions have not been reported in the absence of silver salts,[62] even in aqueous media.[18,19,21] Gold catalysis in water was shown to be possible in the absence of silver salts,[15a,63] which are often added as activating agents, in particular to generate active cationic species. To better understand the level of ionization of both **5α** and **5β** complexes in water, measurement of molar conductivities after 2 and 72 h of solubilization of the complexes in deionized water were made. This study demonstrated the partial but significant ionization of both **5α** and **5β** complexes since Λ values ranging from 29.1 to 43.9 $S.cm^2.mol^{-1}$, consistent with the formation of active cationic Au^I complexes in H_2O, were observed (Figure and Table S2 in the supporting information). Therefore, this suggests that the lack of activity observed in the absence of silver salts in enyne cyclization is likely not related to low ionization of (**ICyD^{Me}**)AuCl **5α** complexes but rather to a possible implication of silver in the mechanism of the reaction.[64]

The hydroxycyclization reaction of enyne **30** was also tested with both (**ICyD^{Me}**)AuCl catalysts in pure water (Scheme 7).[65] In a first set of reactions performed in the presence $AgSbF_6$, both α-CD and β-CD-derived catalysts **5α** and **5β** were found to be efficient in forming the expected cyclized alcohol **31**, which was isolated in 74 and 63% yield, respectively (Table 6, entries 1-2). In addition, the β-CD-derived catalyst **5β** was also found to induce a high control of enantioselectivity, leading to the formation of **31** with 95% *ee* (entry 2). A second set of experiments was conducted in the absence of silver salts (entries 3-6). No conversion was observed with **5α** (entry 3). However, when **5β** was used, the hydroxycyclization product **31** was obtained at room temperature in up to 79% yield and 98% *ee* (entries 4 and 5). Increasing the temperature to 50 °C allowed to significantly decrease the reaction time to 4 h to give **31** in 74% yield while keeping the same level of enantioselectivity (ee 96%, entry 6). Therefore, the results show that no silver salts are required in the hydroxycyclization reaction, in contrast to the previous enyne cycloisomerization reaction, and that high enantioselectivity is obtained in water.

Scheme 7. Enantioselective hydroxylation-cyclization reaction of 1,6-enyne **30**.



30 **31**

Table 6. Enantioselective hydroxylation-cyclization reaction of 1,6-enyne **30** in pure water.

Entry	Ligand	Complex	Additive	*T* (°C)	*t* (h)	Yield (%)[a]	*ee* (%)[b]
1	α-**ICyD^{Me}**	**5α**	$AgSbF_6$	50	18	74	54 (-)

2	β-**ICyD^{Me}**	**5β**	$AgSbF_6$	20	18	63	95 (-)
3	α-**ICyD^{Me}**	**5α**	-	50	40	1	-
4	β-**ICyD^{Me}**	**5β**	-	20	23	47	98 (-)
5	β-**ICyD^{Me}**	**5β**	-	20	45	79	97 (-)
6	β-**ICyD^{Me}**	**5β**	-	50	4	74	96 (-)

[a] Isolated yields; [b] Enantiomeric excess determined by chiral HPLC.

Conclusion

A series of water-soluble complexes with encapsulated copper(I), silver(I) or gold(I) centers were obtained by covalent capping of permethylated CDs with NHC ligands. The corresponding (**ICyD^{Me}**)MCl were found to have different catalytic behaviors in water with an important effect of the nature of the CD (α or β). The use of the smaller α-**ICyD^{Me}** ligand in most cases induces a decrease in reactivity due to steric bulk, but at the same time induces an increase of stability of the metal complex. For instance, this allowed efficient hydration reaction of alkynes with (α-**ICyD^{Me}**)AgCl **5α** whereas (β-**ICyD^{Me}**)AgCl **5β** is inactive due to degradation of the metal complex. In contrast, both **5α** and **5β** gold complexes are stable and active in hydration reactions. More generally, (β-**ICyD^{Me}**)AuCl **5β**, in which the CD cavity is larger, was found to be a very efficient and selective catalyst in gold-catalyzed reactions. The size of the cavity clearly matters as larger substrates react significantly faster with β-**ICyD^{Me}** affording some degree of substrate selectivity for α-**ICyD^{Me}** with methanol as co-solvent. Hydroarylation reactions in pure water were also performed and found to be regioselective. Finally, these water-soluble complexes induce high control of enantioselectivity in gold-catalyzed cycloisomerizations in water giving up to 81% ee and **5β** was found to be particularly efficient in promoting the enantioselective hydroxycyclization reaction of 1,6-enynes, leading to the cyclized alcohols in up to 98% ee. **ICyD^{Me}** are therefore useful ligands for selective catalysis in pure water that will be further explored.

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