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A Remarkably Simple Hybrid Surfactant–NHC Ligand, Its Gold-Complex, and Application in Micellar Catalysis

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Abstract: A combination of an N-heterocyclic carbene (NHC) ligand and a structurally simple surfactant has been realized, the hybrid surfactant–NHC. The related gold complex was synthesized, fully characterized, and applied in catalysis. This remarkably simple strategy allows, in combination with a co-surfactant, the application of gold catalysis in water.

Nowadays the majority of reactions in organic chemistry are conducted in organic solvents, often to ensure a good solubility of the reaction partners and catalysts. Therefore, organic solvents account for the biggest part of the waste generated during the reaction and its workup.[1] Hence it is highly desirable to reduce the amount of required solvent, or as an alternative to use more environmentally friendly solvents, with water, as Nature's favorite solvent, being a logical and green choice.[2] Different approaches were established to transfer organic reactions into water as the reaction medium, including phase-transfer catalysis,[3] water soluble catalysts,[4] and micellar arrays,[5] which mimic organic solvents as the reaction medium. Micellar arrays are spontaneously formed by amphiphilic species (surfactants) in water even at very low concentrations.[6] Well-studied and established surfactants, for example, are sodium dodecyl sulfate (SDS) and TPGS-750 M,[7] a tailor-made surfactant established by Lipshutz et al.

Several reports describe the incorporation of metal catalysts in micellar arrays using, for example, phosphines and amines as ligands.[8] However, only a few publications describe the use of N-heterocyclic carbenes (NHCs) as ligands in micellar catalysis.[9] In terms of metallosurfactants there is only one single report, describing the use of a metal–NHC species. In this case, the NHC is bound by the metal to the surfactant, and the properties of the rather complex surfactant are unrelated to the NHC ligand.[10] As our group is interested in the design and application of NHCs in new and undescribed fields, not only in the term of catalysis, we envisioned combining the properties of a surfactant with an NHC, thus forming a new hybrid surfactant–NHC ligand. This new ligand would allow the interaction with a much simpler and commercially available surfactant and still offer the characteristic advantages of the NHC ligands (Figure 1).[11] The main advantage offered by this system would be the separation of the hydrophobic part of the surfactant and the nitrogen substituents, thus allowing on demand modifications of the ligand head group without influencing the properties of the surfactant, which are located in the backbone of the ligand.

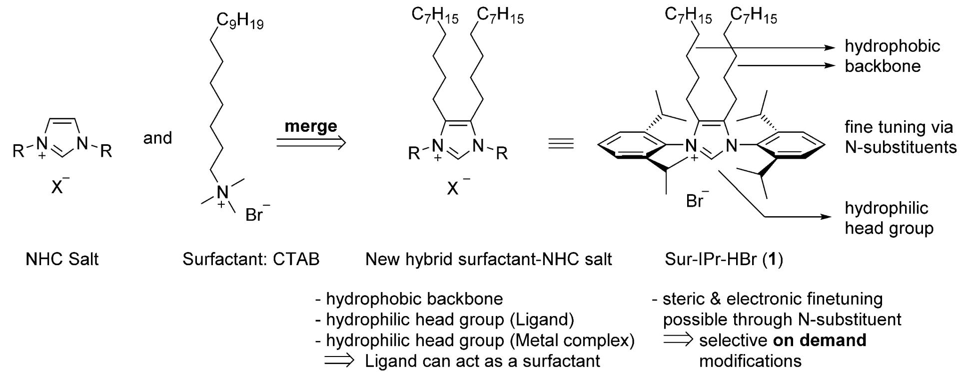

Figure 1. Combination of an NHC ligand and a surfactant.

Based on our recent report on NHCs[12] with long alkyl chains in the backbone for the stabilization of nanoparticles, we decided to combine the cationic surfactant CTAB and the NHC IPr for three reasons:

1) CTAB together with SDS is one of the cheapest commercially available surfactants and is well understood;[13] additionally it offers the same charge as IPr·HCl at the head group.
2) IPr, which has been studied in detail, is stable as a free carbene, and forms robust and catalytically active complexes with gold.[14]

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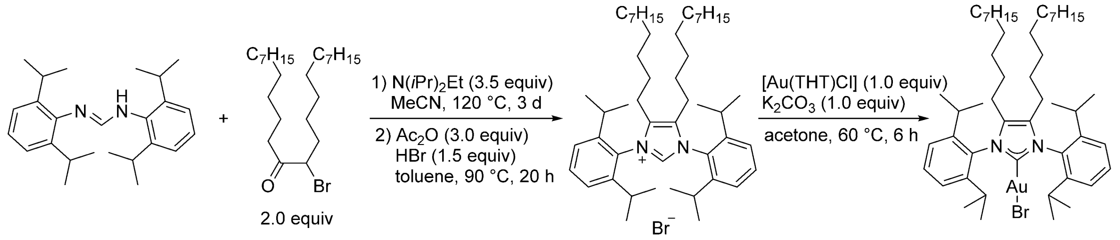


2 **3** **1** **4**

Scheme 1. Synthesis of the hybrid surfactant–NHC ligand **1** and the corresponding gold-complex **4**. THT = tetrahydrothiophene.

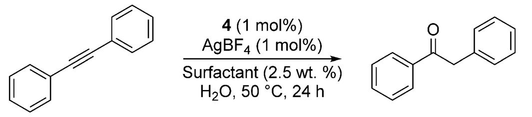
3) The head group and backbone would offer an orthogonal and simple set of signals by NMR spectroscopy, which would simplify the analysis, under micellar conditions.

The new hybrid surfactant–NHC ligand **1** can be easily synthesized by a two-step, one-pot procedure starting from formamidine **2** and α-bromoketone **3** in a moderate 75 % yield.[15] The corresponding Au^I-complex **4** was then prepared in 86 % yield by using a procedure reported by Nolan et al. (Scheme 1).[16]

The new complex is air and moisture stable for months and was fully analyzed. We moved on and tried to apply **4** as a catalyst in a micelle, to prove our concept of combining a NHC and a surfactant in one ligand to be valid. We chose the hydration of 1,2-diphenylacteylene to be our benchmark reaction for two main reasons: 1) Nolan et al. showed with this reaction the tremendous potential of Au^I–NHC complexes in catalysis[17] and 2) as the reaction is carried out in aqueous media it offers the perfect opportunity to test and compare our micellar approach.

In the initial test reaction 1,2-diphenylacetylene was reacted in the presence of 1 mol % (**4**), 1 mol % $AgBF_4$, and 2.5 wt. % of a given surfactant (Table 1). When a cationic (Table 1, entry 2) or a neutral surfactant (entries 1 and 4) was used, no reaction or only low conversion could be observed, while the anionic surfactant (entry 3) showed a conversion greater than 95 %. The anionic head group seems to be crucial for the cationic Au^I complex to insert into the micelle, as an attractive interaction between the positive and negative charges is beneficial. In comparison, the cationic Au^I complex and a positive surfactant's head group could repel each other. Control experiments (entries 5 to 7) showed that all three components are necessary for the reaction. If the surfactant was used in amounts below the CMC (critical micelle concentration) (entry 8) only traces could be observed by GCMS, an indicator that a micelle is needed for reactivity. Applying the standard gold complex [Au(IPr)Cl] ended up in only trace amounts of product (entry 11). This strengthens our hypothesis about the interaction between the surfactant and the cationic Au^I complex, which is generated in situ from **4** and $AgBF_4$. Without the two long alkyl chains in the backbone of the ligand no interaction between the hydrophobic parts is feasible and therefore no incorporation into the micelle is possible. Further optimization studies showed that a surfactant concentration as low as 0.5 wt. % is sufficient for a conversion greater than 95 % (entry 9). With the optimized conditions in hand, we focused on the substrate scope of our transformation (Scheme 2). Desoxybenzoin **5a** was obtained in high yield, and could be even increased to 94 % on a 5 mmol scale with a reduced catalyst loading of only 0.1 mol %. This demonstrates the high efficiency and robustness of our hybrid surfactant–NHC approach. Only moderate yields between 30 to 59 % (**5b**–**e**) were obtained, when the starting material was a terminal alkyne. An exception in this case was **5k** with a high yield of 89 %. The functional-group tolerance of our transformation represents a nice feature set for further functionalization, esters (**5g**, 61 %), bromines (**5h**, 82 %), protected amines (**5j**, 85 %), and alcohols (**5l**, 87 %) were tolerated without problems and the corresponding products were obtained in moderate to high yields.

Table 1. Initial screening.[a]



Entry	Surfactant	**4**/$AgBF_4$ [mol %]	Conversion [%][b]
1	DPPC	1	15
2	CTAB	1	0
3	SDS	1	> 95
4	TPGS-750-M	1	trace
5	SDS	no $AgBF_4$	trace
6	SDS	no **4**	trace
7	–	1	trace
8[c]	SDS	1	trace
9[d]	SDS	1	> 95
10[e]	SDS	1	0
11[f]	SDS	1	trace

[a] DPPC = dipalmitoylphosphatidylcholine; CTAB = cetyltrimethylammonium bromide. TPGS-750 M = DL-α-Tocopherol methoxypolyethylene glycol succinate. All reactions were run on a 0.5 mmol scale at a substrate concentration of 1 M. [b] Determined by GCMS. [c] With 0.125 wt. % SDS (below CMC of SDS). [d] With 0.5 wt. % of SDS. [e] Reaction performed at room temperature. [f] Standard [IPrAuCl] was used instead of **4**.

Assuming that the mechanism of this transformation is equivalent to the one in organic solvents,[18] the type of self-assembly and interaction remains unclear. To answer these questions we conducted three sets of experiments. At first dynamic-light scattering (DLS) measurements provided insight if a change of size occurs, when the SDS micelles are interacting with either **1** or **4** (Figure 2). In both cases a clear formation of

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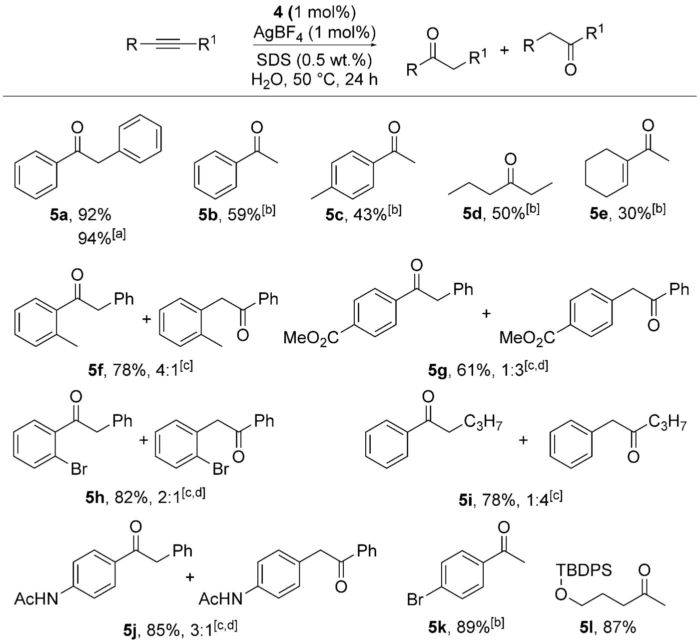

Scheme 2. All reactions were run on a 0.5 mmol scale at a substrate concentration of 1 M. Given yields, are isolated yields; [a] Reaction performed on a 5 mmol scale with 0.1 mol% [Au] and [Ag] at 80 °C for 2 days. [b] Yields determined by GC-FID with Mesitylene as the internal standard; [c] Ratio determined by ^{1}H NMR spectroscopy. [d] 2 mol% of [Au] and [Ag] used, reaction run for 2 days.

a larger species, potentially two, is visible. Notably the species look to be the same for **1** and **4**, which indicates a similar interaction between SDS and our surfactant ligand or the related gold metallosurfactant. Next we performed film balance measurements to prove the attractive interaction between SDS and **1** or **4**. If a stable film formation is viable electrostatic interactions demand a head-to-head assembly of SDS and **1** or **4** (Figure 3). SDS and **1** clearly form a stable film in a two to one mixture, which is indicated by the plateau in the surface pressure at higher pressure. The combination of SDS and **4** shows not such a clear plateau, but still a change in the slope at higher pressure, which proves the film formation. As **4** bears a less polar head group than **1**, this result is expected. However, keeping in mind that the active complex during the catalysis is positively charged like **1**, a stronger interaction in comparison to **4** is viable. From the results of DLS and film balance measurements we can conclude that, under the reaction conditions the formation of a mixed micelle, with a head-to-head orientation of the two components is the most likely scenario. At last we wanted to address the level of immersion of the active gold complex into the micelle. Therefore, we synthesized derivatives of **4** with different chain lengths (shorter: C_7H_{15}; longer: $C_{15}H_{31}$) in the backbone and measured kinetics of our standard reaction (Figure 4). A short chain in the backbone of our hybrid surfactant-NHC would force the gold atom of **4** to be immersed in the micelle while a long chain would bring the gold atom out of the micelle. In both cases the reaction rate should decrease, as the two reactants get separated. If the chain length is optimal the gold atom would be placed directly in the boundary layer of the micelle and the highest reaction rate should be observed.

As assumed, the cationic **4** shows the highest reaction rate, which indicates that the gold atom is located in the boundary layer of the micelle. To support our hypothesis that we create mixed micelles with

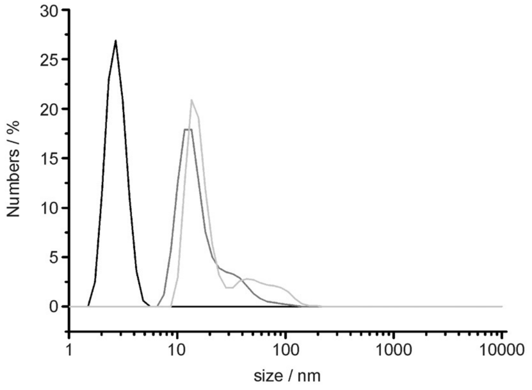

Figure 2. DLS measurements of SDS and in combination with **1** or **4**. ——: SDS pure; ——: SDS, Sur-IPr-HBr (2:1); ——: SDS, Sur-IPr-Au-Br (2:1). Milli-Q. Water (pH 5.6) 3.3 cm^2 min^{-1}, 20 °C.

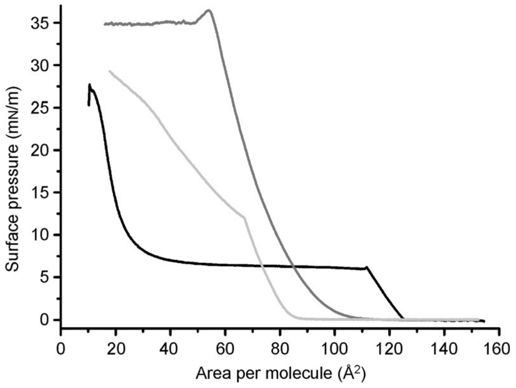

Figure 3. Film balance measurements of SDS and in combination with **1** or **4**. ——: SDS pure; ——: SDS, Sur-IPr-HBr (2:1); ——: SDS, Sur-IPr-Au-Br (2:1).

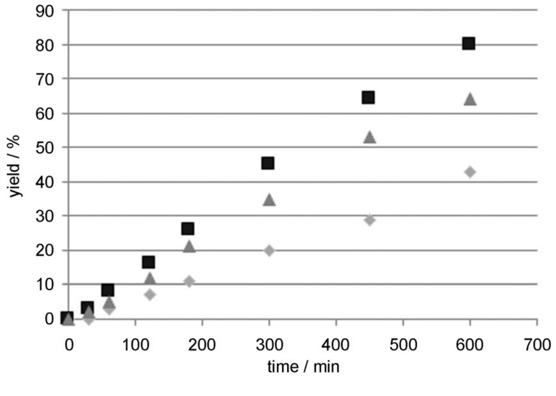

Figure 4. Kinetics of our model reaction with different alkyl chain lengths. ◆: C7-IPr; ■: C11-IPr; ▲: C15-IPr.

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a head-to-head assembly with a size of about 10 to 20 nm, we measured a TEM image of our micelles (Figure 5). The TEM image clearly shows ring-shaped objects with a size between 10 and 20 nm. The dark rings can be related to the surfaces of the micelles in which the gold is located. As gold shows a higher contrast in comparison to carbon, only the surface of the micelle should be dark, which is true for our TEM images.

Overall we have developed a new type of NHC ligand, which successfully combines the advantages of surfactants and NHC ligands, to adapt classical organic chemistry into the field of micellar chemistry and catalysis. Furthermore other applications in the field of membrane interactions and organometallic drug design could be rationally addressed with such a powerful and modifiable ligand.

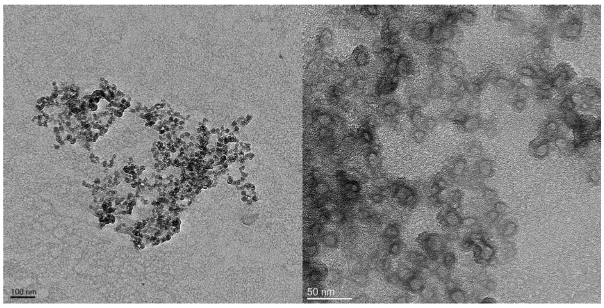

Figure 5. TEM image of the micelles (left: overview with 100 nm scale bar; right: zoom with a 50 nm scale bar).

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Keywords: gold catalysis · green chemistry · micelles · N-heterocyclic carbenes · surfactant

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