PROJECT: MODUCAT (Marie Curie International Incoming Fellowship - FP7-PEOPLE-IIF-2008 - Grant Agreement number PIIF2-GA-2009-909423)

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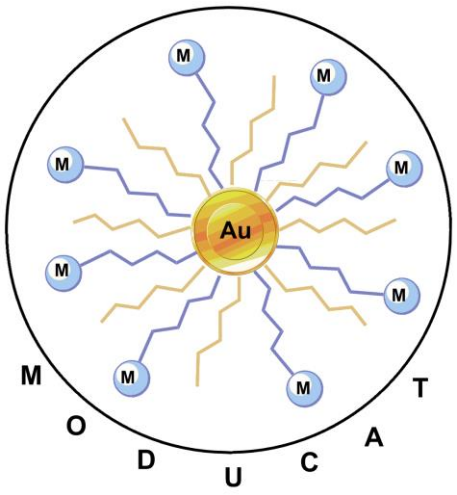
Project Coordinator Name: Prof. Nikolai Ustynyuk

Project Coordinator Organisation Name: A.N. Nesmeyanov Institute of Organoelement Compounds of the Russian Academy of Sciences



1. PUBLISHABLE SUMMARY

The need for sustainable, clean methods to produce fine chemicals for use as pharmaceutical intermediates or drugs, avoiding the production of large quantities of waste and toxic solvents, has received during the last twenty years large attention from both academic and industrial worlds. Homogeneous catalysts, based on selected transition metals and tailored organic ligands, are considered as the most promising approach to produce large quantities of such important derivatives. By definition, a catalyst can bring about the transformation of large amounts of starting material (substrate) into the desired products without formally taking part into the reaction. As the interaction of drugs with the living organisms often involves only one of the possible non-superimposable forms of a molecule (the so called "enantiomer"), this means that also the catalysts used to produce such transformation must select which enantiomer to give, in other words must "induce chirality" being an "asymmetric catalyst". A drawback in the application of such technology is the complicate synthetic protocols and the high costs of optically pure ligands and transition metals, together with the fact that these homogeneous catalysts (i.e. soluble in the reaction media) can be rarely recovered and reused, worsening their cost effectiveness.

Thus, replacing conventional methods with new approaches involving asymmetric catalysis is mandatory to reduce considerably energy/materials costs and the environmental impact of chemical manufacturing. The improvement of both efficiency and selectivity of traditional molecular chiral catalysts is a time consuming and expensive procedure that may be bypassed by the development of the innovative "**modular catalysts**". MODUCAT project has therefore focused on this task.

The main objectives of the Project are: (1) to develop the modular assembly of a chiral catalyst consisting of two independent units, separately responsible for activity and enantioselectivity. Such units, assembled together by Coulombic and hydrophobic interactions, should form an innovative catalyst conjugating activity with enantioselectivity; (2) to validate the MODUCAT methodology in model catalytic asymmetric processes carried out in aqueous media. While the few known examples of "modular catalysts" find application in non-polar media, we proposed to use chiral micelles and/or nanoparticles (NPs) functionalized with self-assembled monolayers (SAMs) of optically active charged molecules to bring about the modular approach in polar solvents. This will avoid the use of large quantities of often toxic organic solvents.

In the Project we realized the idea of preparing chiral modular catalyst for a given catalytic process, asymmetric transfer hydrogenation (ATH) of acetophenone (Acp), based on assembly of oppositely charged achiral catalytically active complexes and nanoscopic chiral units. Specifically designed charged nanoscopic objects (NPs and micelles) were assembled with organometallic catalysts in aqueous solutions by means of Coulombic (ES) and van der Waals (vdW) forces to give new entities having the properties of both units. Such modular catalysts being simply an ad-mixture of the two components, was shown to convert Acp into chiral 1-phenylethanol in water. Although the enantiomeric excess (*ee*) reached so far is

moderate (up to 16%), proof of concept was established, allowing us to extend the modular catalysis approach to aqueous media.

In the first part of the project, gold NPs functionalized with thiolate SAMs were studied. They were shown to be convenient models to study assembly of oppositely charged nanoscopic objects and catalyst precursors. The aggregation of AuNPs, as a result of their complexation with the catalyst, was monitored by spectroscopic analyses such as UV-vis assisted titrations. This technique exploits the intensive Surface Plasmon Resonance (SPR) band of AuNPs, giving information on the size of the NP/catalyst aggregates. Such information is important to design properly the catalyst auxiliary group, which is responsible for binding with the NP. In this way, we demonstrated that only the catalysts bearing quaternary ammonium groups with long alkyl chains (C_{16}) are able to form stable complexes with AuNPs having as SAM derived from 11-mercaptoundecanoic acid (MUA) coupled with aminoacids (Figure 1). Analysis of the corresponding SPR band gives information on both the stability of the binary NP/catalyst aggregates and of their colloidal form in solution, which in turn helps to determine the applicable range of NP/catalyst ratios to be employed in the real catalytic system.

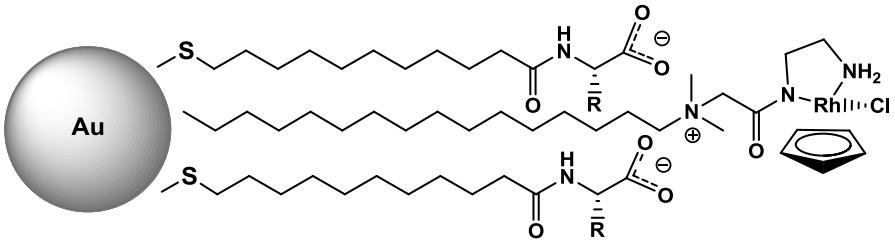


Figure 1. A pictorial view of Au-based NP carrying thiolate SAM ending with an aminoacid group. The active catalyst is obtained by interpenetrating a long alkyl chain of ammonium group into a chiral thiolate monolayer. Such complex is stabilized by attractive both hydrophobic ($CH_2 \ldots CH_2$) and Coulombic (COO^-/N^+) forces.

Some drawbacks of this approach however emerged. First of all, it was not possible to use Circular Dichroism (CD), the common technique available for such studies, for measuring transfer of chirality information from chiral NP to achiral catalyst in the complex formed. This was due to the presence of intensive SPR band and inter- and intra-band transitions in visible and near UV regions of the spectrum of the metal NPs. Another disadvantage of using NPs as a chiral inductor is that the colloidal stability of the modular catalyst is significantly decreased by strong vdW attraction between NPs, due to their metallic nature. Ultimately, although the densely charged SAM of AuNPs is required to obtain high stability in water, it also prevents the hydrophobic substrate from approaching the chiral surface and the catalytic center, thus inhibiting enantioselective catalysis. In conclusion, despite the NPs are convenient models for our studies, in order to develop the modular approach in water, they appeared to be inapplicable in real catalytic systems.

On this basis, in the second part of the project we employed chiral micelles as chiral inductors in the real catalytic systems. Micelles, although similar to NPs in their structure, have an "empty" space instead of a metal core. This difference is an advantage for modular catalysis as: 1) they should be able to store the hydrophobic substrate inside the micelle and enhance the interfacial substrate/catalyst/reagents transfer; 2) they should be able to re-assemble dynamically to release the substrate directly to the chiral and catalytically active surface of the micellar catalyst; 3) they should be stable in solution in wide range of catalyst/micelle ratios, ionic strengths and pH range, since vdW forces between micelles are negligible compared to NPs; 4) CD measurements can be used to read the chirality transfer information from the catalyst/micelle binary aggregates.

All these advantages make chiral micelles the most promising chiral additives to deliver chirality into an achiral catalyst without affecting its activity. In fact, this is the way how the biological systems work in living organisms. In our experiments we showed that replacement of chiral NPs with chiral micelles gives indeed a modular catalyst (Figure 2), which may be both active and enantioselective in ATH of Acp in water. The transfer of chirality information inside such binary catalyst is hardly predictable and still have to be thoroughly studied; the degree of enantioinduction should be improved by careful design of both the catalyst's and the micelles' structures. We have demonstrated that the efficiency of enantioinduction strictly depends on the separation distance $M \ldots N^+$ between the active

metal center M and the ammonium function N^+, which is closely connected to the distance M…C* between M and the chiral group C* of the inductor. The shorter the M…N^+ distance, the higher enantioinduction (*ee*) could be expected. The structure of the chiral inductor also plays an important role in modular catalysts, and more than one stereogenic center is probably required. In conclusion, the results obtained so far prove unambiguously that the modular catalysis methodology can be achieved.

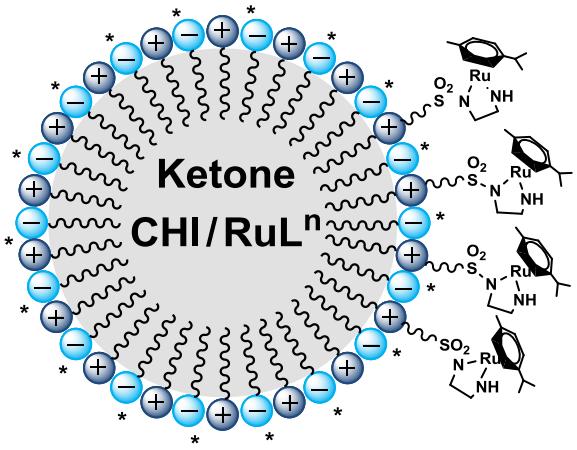


Figure 2. A schematic drawing of the modular assembly (catanionic chiral micelle) consisted of negatively charged chiral surfactants and achiral surface active catalyst.

In summary, the work done in the MODUCAT project by the researcher has provided the validation of the applicability of the concept of modular catalysis for catalytic processes in water. This methodology provides a realistic approach for preparing binary catalysts in polar and aqueous media, thus waving the major drawback towards the application of "modular catalysis" to sustainable chemistry. The development of an innovative chemical approach for the design of catalytic systems for asymmetric synthesis is going to contribute to the development of sustainable chemistry, of potential interest or industrial applications in fine chemical manufacturing on a large scale, as it suggests an environmentally benign methodology based on the design of a new generation of inexpensive, less time consuming, less laborious and environmentally friendly asymmetric catalysts.