## Tandem Catalysis in Supramolecular Cages

Chemical reactions can transform substrates to useful products. Many of these reactions require the use of a catalyst in order to lower the reaction temperature or pressure, and increase the selectivity of the reaction towards the desired products. A catalyst increases the rate of a chemical reaction by lowering the activation energy without being consumed itself. Transition metal catalysts consist of a metal center surrounded by a ligand. The chemical structure of the ligand can induce steric and electronic changes at the metal center in order to alter the activity and selectivity of the transition metal catalyst.

Generally, the production of useful products requires more than one (catalytic) reaction step. In order to improve the ecological and economical footprint of synthetic chemistry, strategies to combine catalytic reactions into one synthetic operation have been developed. Combining two independent catalytic cycles that are operating simultaneously to sequentially modify a substrate into the desired product is known as orthogonal tandem catalysis. Performing the two catalytic reactions in a single reaction vessel requires only one workup or purification procedure (Figure 1).


*Figure 1: Orthogonal tandem catalysis scheme with 2 catalytic cycles. The substrate is converted by catalyst 1 to the intermediate, that is subsequently converted by catalyst 2 to form the final product.*

The combination of two catalytic cycles into a single reaction vessel comes with its own set of challenges, as compatibility of the reagents, catalysts and reaction conditions has to be achieved. The application of one of Nature's strategies to overcome these incompatibilities has been investigated, which involves tandem catalysis making use of compartmentalization of one or both catalysts.

In **Chapter 1** an overview is given of compartmentalization strategies used in homogeneous catalysis to achieve tandem catalytic transformations. The concepts are described that spatially separate the two catalysts, consisting of combinations of enzymes, transition metal catalysts and organocatalysts. The spatial separation, in many cases achieved by encapsulation of at least one of the catalysts, is required to achieve tandem catalysis due to the incompatibility of the catalysts that leads to

catalyst deactivation in the absence of compartmentalization. The encapsulation of transition metal complexes in supramolecular cages has been studied and was shown to alter reactivity, selectivity and stability of the catalysts. An example of the effects of encapsulation in supramolecular cages on gold catalysis is provided in **Chapter 2**. **Chapters 3-5** summarize our investigations that aim to expand the understanding of the principles of encapsulation of catalysts in supramolecular cages as a strategy for tandem catalysis.

In **Chapter 2** chiral gold catalysts were encapsulated in a supramolecular sphere in order to study the effects of the spatial confinement caused upon encapsulation on the chirality transfer of the gold catalyst. The spatial separation between the chiral phosphine ligand and the substrate often limits the transfer of chirality from the chiral phosphine to the substrate that is cyclized. Encapsulation in a self-assembled hexameric resorcin[4]arene capsule was applied to pre-organize the substrate and the catalyst in a sterically confined interior of the supramolecular capsule (Figure 2). The encapsulation of the chiral gold catalysts was shown to lead to increased reaction rates for the cyclization of 1,6-enyne substrates. It was also found that with a match of the size of the chiral phosphine ligand and the 1,6-enyne substrate in the interior of the supramolecular capsule, the enantio-induction of the chiral phosphine ligand onto the cyclized product could be enhanced. The enantioselectivity of chiral gold catalysis is improved upon encapsulation of the gold catalysts inside the hexameric resorcin[4]arene capsule.

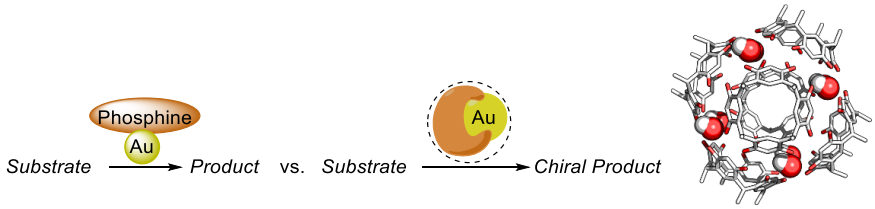


*Figure 2: The gold catalyzed cyclization of a substrate towards its product is studied upon encapsulation of the gold-phosphine in the resorcin[4]arene capsule (schematically depicted as the dashed circle, see insert) in order to enhance the enantioselectivity of the cyclization reaction towards the formation of a chiral product.*

Combining two transition metal catalyzed reactions in a tandem catalytic process can lead to incompatibility of the catalysts with each other or with the reagents required for both reactions. **Chapter 3** describes the compatibility issues that arise in transition metal tandem catalysis for three combinations of rhodium, cobalt and gold catalyzed tandem catalytic systems (Figure 3). Whereas the rhodium and cobalt catalyzed reactions proved to be mutually compatible, the design of a

substrate that can be consecutively transformed by both catalysts and finding appropriate reaction conditions of the tandem catalytic system showed to be the main challenge. The combination of a cobalt and gold catalyzed reaction turned out to be mutually incompatible because the applied gold catalyst is rapidly deactivated by the reagents required for the cobalt catalyzed transformation.

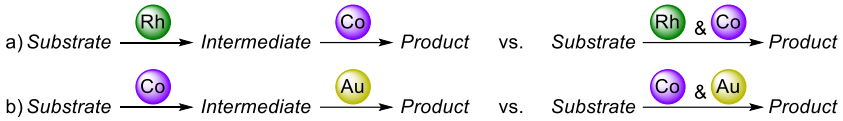


*Figure 3: a) The rhodium catalyzed hydroformylation of a substrate forms an intermediate that can undergo a cobalt catalyzed carbene carbonylation reaction to form the desired product. The tandem catalytic combination of rhodium and cobalt catalyzed reactions on several substrates were studied. b) A cobalt catalyzed carbene carbonylation of a substrate is combined with a gold catalyzed cyclization of the intermediate to form the desired product. The tandem catalytic combination of cobalt and gold catalyzed reactions was studied.*

The strategy of catalyst encapsulation as studied in Chapter 2 was applied to overcome some of the challenges of tandem catalysis as described in Chapter 3. Using a supramolecular encapsulation strategy of transition metals to obtain control over compatibility, selectivity and reactivity in tandem catalysis was applied in **Chapter 4**. The effects of catalyst encapsulation on the size-selectivity in catalysis were studied for ruthenium and gold catalysis. Encapsulation of a ruthenium metathesis catalyst in a hexameric resorcin[4]arene capsule was shown to influence the activity of intermolecular metathesis reactions and led to substrate selective transformations (Figure 4). Combining the supramolecularly controlled metathesis reaction with a gold catalyzed cyclization reaction was, however, unsuccessful due to incompatibility of the applied ruthenium catalysts with the substrate of the gold

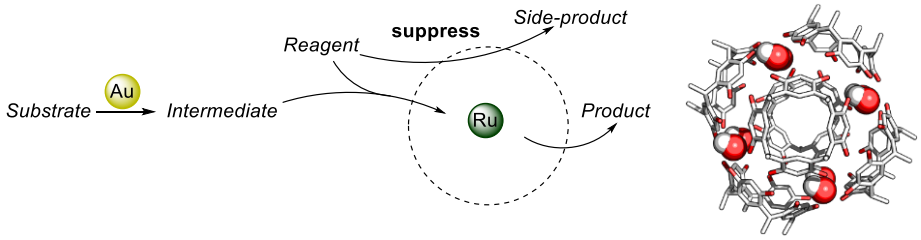


*Figure 4: Gold catalyzed cyclization of the substrate forms the intermediate. This intermediate can undergo a ruthenium catalyzed cross-coupling metathesis with a reagent to form the desired product. Upon encapsulating the ruthenium catalyst, the formation of the side-product from the homo-coupled reagent is suppressed. The dashed circle indicates the supramolecular hexameric resorcin[4]arene capsule (see insert).*

catalyzed cyclization reaction. Cyclization of a 1,6-enyne substrate followed by a cross-coupling metathesis reaction with styrene was achieved using only the ruthenium catalyst, in the absence of the gold catalyst or supramolecular capsule.

**Chapter 5** discusses our attempts of combining an organocatalyzed aldehyde to alcohol conversion with a gold catalyzed cyclization reaction in a supramolecular $M_{12}L_{24}$ metallocage to achieve a tandem catalytic reaction benefitting from supramolecular catalyst pre-organization (Figure 5). The pre-organization of the two catalysts within the same sphere is anticipated to enhance the efficiency of a tandem catalytic reaction by circumventing unstable intermediates to react in the bulk solution.

The proline catalyzed aldol reaction and gold catalyzed cyclization could be performed simultaneously under the same reaction conditions. Even though the addition of a base for the deprotonation of the sulfonated prolineamide catalyst showed to be detrimental to the gold catalysis, encapsulation in a $M_{12}L_{24}$ sphere

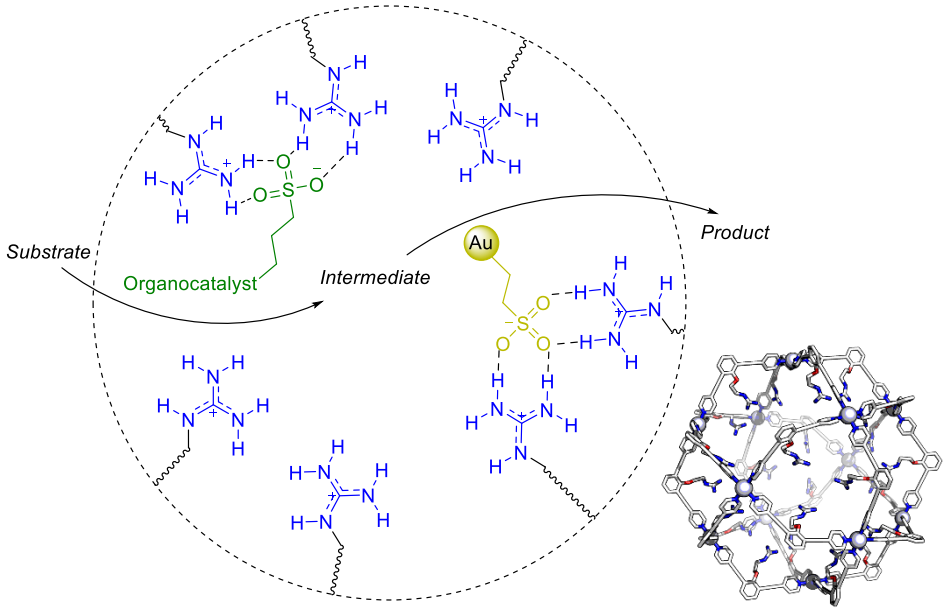


*Figure 5: Schematic representation of a tandem catalytic system taking place inside a $M_{12}L_{24}$ guanidinium sphere (see insert). The organocatalyst and gold catalyst are coordinated via a sulfonate group to the endohedral guanidiniums (blue) of the sphere. The substrate undergoes an organocatalyzed reaction to form an intermediate that can subsequently be cyclized by the gold catalyst to form the desired product.*

solved this problem. The substrate was, however, not able to undergo both catalytic transformations consecutively under the applied tandem catalytic reaction conditions.
A sulfonated pyridinium aldehyde organocatalyst was used for the hydrate formation of an aldehyde into the gem-diol in the presence of water to be subsequently coupled to a gold catalyzed cyclization reaction. Simultaneous encapsulation of both catalysts inside of the same $M_{12}L_{24}$ sphere was shown to facilitate tandem catalysis of the aldehyde to hydrate formation and subsequent cyclization to yield the desired tandem catalytic product in the $M_{12}L_{24}$ spheres. Further optimization of the reaction conditions is required to improve these results that already show that tandem catalysis within a $M_{12}L_{24}$ sphere is feasible with an intermediate that is too unstable to be isolated by itself.

The effects of encapsulation of several transition metal catalysts in supramolecular cages have been studied and applied in tandem catalysis. Tandem catalytic systems in the absence of encapsulation, upon encapsulation of one catalyst and upon the encapsulation of both catalyst have been studied. To provide proof of concept a substrate is required that is able to perform both consecutive transformations without inhibiting the present catalysts. The simultaneous encapsulation of two catalysts within the $M_{12}L_{24}$ guanidinium sphere shows the potential advantage of applying an encapsulation strategy in tandem catalysis to obtain new products. Otherwise too reactive and unstable intermediates can be immediately converted when encapsulating both catalysts inside a supramolecular cage, thereby preventing their consumption in the bulk solution. Further optimization of the systems is required, but their potential to be applied in useful chemical transformations has been shown.