A Switchable Gold Catalyst by Encapsulation in a Self-Assembled Cage

Jans, A.C.H.; Gómez-Suárez, A.; Nolan, S.P.; Reek, J.N.H.

Published in:
CHEMISTRY-A EUROPEAN JOURNAL

DOI:
10.1002/chem.201603162

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: https://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Supramolecular Chemistry

A Switchable Gold Catalyst by Encapsulation in a Self-Assembled Cage

Anne C. H. Jans,[a] Adrián Gómez-Suárez,[b] Steven P. Nolan,[c, d] and Joost N. H. Reek*[a]

Abstract: Dinuclear gold complexes have the ability to interact with one or more substrates in a dual-activation mode, leading to different reactivity and selectivity than their mononuclear relatives. In this contribution, this difference was used to control the catalytic properties of a gold-based catalytic system by site-isolation of mononuclear gold complexes by selective encapsulation. The typical dual-activation mode is prohibited by this catalyst encapsulation, leading to typical behavior as a result of mononuclear activation. This strategy can be used as a switch (on/off) for a catalytic reaction and also permits reversible control over the product distribution during the course of a reaction.

There is a growing interest in transition-metal catalysis in confined spaces as the approach provides an additional tool to control selectivity and activity in catalysis. For example, it has been demonstrated that the encapsulation of rhodium complexes in a hemispherical porphyrin assembly results in catalysts with increased activity and unprecedented branched selectivity in the hydroformylation of terminal and internal alkenes. In addition, the encapsulation of transition-metal complexes in preformed cavities through weak interactions can lead to unexpected reactivity: $\text{M}_{1}\text{L}_{2}$ anionic tetrahedral capsules, for instance, can host cationic organometallic catalysts in their hydrophobic cavities, thereby inducing substrate selectivity. Moreover, reaction rates and product distribution can be greatly affected by catalyst encapsulation. Interestingly, many catalytic reactions operate through a dinuclear mechanism or deactivate via a dinuclear pathway by encapsulation of a transition metal complex, such decomposition pathways can be suppressed, leading to higher catalytic turnover numbers.

In principle, an encapsulation event could also change the catalytic pathway of a reaction, and as such can be used as a switch for a catalytic transformation. Switchable catalysis is an interesting upcoming field of research as it provides new tools to control the reaction process with external stimuli such as light, pH, or metal coordination, a concept that is important to control reactions in nature. In a recent study, encapsulation of a photoredox catalyst was shown to be a feasible stimulus to steer reactivity. In a previous paper we reported the encapsulation of an N-heterocyclic carbene (NHC) mononuclear gold(I) complex inside a self-assembled hexameric resorcin[4]arene cage $1_6$ and showed that the encapsulated catalyst gives a different product distribution than the free complex. This supramolecular complex is formed in apolar, water-saturated solvents (Scheme 1). In the current contribution, we report how we change the active gold complex from dinuclear to mononuclear by reversible encapsulation and demonstrate that this can be used for both switching on/off a reaction, as well as for controlling its selectivity during the course of a reaction. Changing the reactivity or selectivity of a gold catalyst has been shown before by changing the ligands or Brensted acid/base effects and even by guest binding by a rotaxane, but reversibly changing the active species of a gold-catalyzed reaction as a result of encapsulation has, to the best of our knowledge, not been shown before.

In this study we use a dinuclear hydroxyl-bridged gold complex ($\text{[Au(NHC)\text{(μ-OH)}]}\text{X}$ instead of a mononuclear gold complex. This complex reacts through different mechanisms...


[a] A. C. H. Jans, Prof. Dr. J. N. H. Reek
Homogeneous, Bioinspired and Supramolecular Catalysis
van ’t Hoff Institute for Molecular Sciences, University of Amsterdam
Science Park 904, 1098 XH Amsterdam (the Netherlands)
E-mail: j.n.h.reek@uva.nl
[b] Dr. A. Gómez-Suárez
School of Chemistry, University of St Andrews, St Andrews, KY16 9ST (UK)
[c] Prof. Dr. S. P. Nolan
Department of Inorganic and Physical Chemistry
Ghent University, Krijgslaan 281 - S3, 9000 Gent (Belgium)
[d] Prof. Dr. S. P. Nolan
Chemistry Department, College of Science, King Saud University
PO Box 2455, Riyadh, 11451 (Saudi Arabia)

Supporting information and authors’ ORCIDs for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201603162.

© 2016 The Authors. Published by Wiley-VCH Verlag GmbH & Co. KGaA. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.
than mononuclear gold complexes\textsuperscript{[20]} and is a privileged catalyst for dual activation reactions.\textsuperscript{[21]} It, however, is too large to fit inside the cage \textit{1}\textsubscript{i}\textsuperscript{[22]} and should be split into mononuclear complexes upon encapsulation. The NHC-Au-X fragment displays the traditional Lewis acidic character of mononuclear cationic gold catalysts, activating unsaturated substrates such as alkynes through \pi\text{-coordinate}, making them more electrophilic and susceptible toward nucleophilic attack.\textsuperscript{[23]} Meanwhile, the NHC-Au-OH species behaves as a Brønsted base and is known to \sigma\-activate substrates such as terminal alkynes or phenols.\textsuperscript{[24]} Together the two species, NHC-Au-X and NHC-Au-OH, can dually activate substrates through both \pi\- and \sigma\-activation (Scheme 2). This dual-activation mode was originally proposed by Toste and Houk\textsuperscript{[25]} and is well established and employed nowadays. In addition, this dual activation has elegantly been explored by Hashmi\textsuperscript{[26]} and Zhang\textsuperscript{[27]} for the formation of gold acetylides, which can react as a nucleophile and attack the \pi\-activated bond of the substrate, and as such represents a common strategy in gold-mediated synthesis.

\begin{equation}
\text{[NHC-Au]} + \text{[Au-NHC]} \rightarrow \text{[Au(NHC)]} + \text{[NHC-Au]} \rightarrow \text{[Au(NHC)]}_{2}[X]
\end{equation}

Scheme 2. Dinuclear complexes [[Au(NHC)]\_2[μ-OH][X]] can dually activate substrates.

We envisioned that encapsulation of the two fragments of the dinuclear gold catalyst [[Au(NHC)]\_2[μ-OH][X]] in separate cages would alter its typical reactivity as they undergo transformations in a site isolated fashion. We anticipated that by complex encapsulation we could reversibly switch between the dinuclear and mononuclear catalyst and, therefore, have a tool to shift from dual gold catalysis to a mononuclear reaction mechanism. This forms the basis for an on/off switchable system, but can also alter the product distribution during a gold-catalyzed transformation.

Indeed, when complex [[Au(Pr)]\_2[μ-OH][BF\textsubscript{4}]] \textit{2} (Scheme 3) and the capsule were mixed together, encapsulation of a mononuclear gold complex was confirmed by \textit{1}H NMR and \textit{1}H DOSY NMR (see the Supporting Information). To demonstrate the principle of switching catalyst activity by selective encapsulation, the dual gold-catalyzed hydrophenolxylation reaction was studied.\textsuperscript{[21,28]} This reaction requires \sigma\-activation of a phenol by the NHC-Au-OH moiety and \pi\-activation of an alkylene by the cationic NHC-Au-X fragment (Scheme 4). Indeed, it was observed that the standard reaction between phenol \textit{4} and diphenylacetylene \textit{5} readily takes place when using \textit{2} as catalyst in the absence of the cage (full conversion within 60 min). However, in the presence of the cage, the dinuclear complex \textit{2} is broken and encapsulated as mononuclear species. As the dual reaction pathway is no longer available, no conversion to vinyl ether \textit{6} is obtained, even after 24 h.\textsuperscript{[29]} We wondered if the reaction could be switched on again by adding a competing guest that would bind more strongly to the cage than the gold catalyst. For this purpose we selected tetralkylammonium salts, as they are known to bind very strongly inside the hexamer.\textsuperscript{[30]} Gratifyingly, upon addition of Et\textsubscript{4}NBF\textsubscript{4} \textit{7} to expel the gold catalyst from the cage, the catalytic activity was restored and product \textit{6} was obtained in 89\% yield after one hour.

Next we explored the cage effect on changing the product distribution of a reaction. For this purpose we explored the conversion of 4-phenyl-1-butyne \textit{8}. Depending on the available reaction pathways, the transformation can yield up to four products (Table 1). In the absence of the cage, \textit{2} can activate two substrates in a \sigma\- and \pi\-activation mode and, therefore, dimerization of \textit{8} takes place through a dual-activation mechanism, yielding the branched and linear products, \textit{11} and \textit{12} respectively (Table 1, entry 1; Scheme 5).\textsuperscript{[26a,30]} As anticipated, this dual-activation reaction pathway is completely blocked upon encapsulation of the catalyst and the production of \textit{11} and \textit{12} stopped. Instead, when in the cage, the catalyst produced the intramolecularly cyclized product \textit{10}, which is known to form via a mononuclear pathway inside the cage (Table 1, entry 2).\textsuperscript{[31]} In the presence of the cage and the competing guest \textit{7}, product \textit{10} was not formed and dimerization products \textit{11} and \textit{12} were obtained (Table 1, entry 3), indicating that under these conditions the catalysis proceeds via a dual-gold mechanism and thus takes place outside the cage.

Due to the presence of water molecules to facilitate the self-assembly of the capsule, the well-documented hydration product \textit{9} was formed in all cases through \pi\-activation of the triple bond\textsuperscript{[31,32]} but only in minor amounts. We observed an in-

\begin{equation}
\text{[Au(Pr)]}_{2}[μ-OH][BF\textsubscript{4}] + \text{[Au(Pr)]}_{2}[μ-OH][BF\textsubscript{4}] \rightarrow \text{[Au(Pr)]}_{2}[μ-OH][BF\textsubscript{4}] \rightarrow \text{[Au(Pr)]}_{2}[μ-OH][BF\textsubscript{4}] \rightarrow \text{[Au(Pr)]}_{2}[μ-OH][BF\textsubscript{4}]
\end{equation}

Scheme 3. Encapsulation of [[Au(Pr)]\_2[μ-OH][BF\textsubscript{4}]] in capsule 1i.

\begin{equation}
\text{[Au(Pr)]}_{2}[μ-OH][BF\textsubscript{4}] + \text{[Au(Pr)]}_{2}[μ-OH][BF\textsubscript{4}] \rightarrow \text{[Au(Pr)]}_{2}[μ-OH][BF\textsubscript{4}] \rightarrow \text{[Au(Pr)]}_{2}[μ-OH][BF\textsubscript{4}] \rightarrow \text{[Au(Pr)]}_{2}[μ-OH][BF\textsubscript{4}]
\end{equation}

Scheme 4. Switching the gold-catalyzed hydrophenolxylation off and on. Reaction conditions: solvent = toluene, T = 80 °C. (4) = 550 mm, (5) = 500 mm, (2) = 2.5 mm (0.025 mol %), [1] = 50 mm.

\begin{equation}
\text{[Au(Pr)]}_{2}[μ-OH][BF\textsubscript{4}] + \text{[Au(Pr)]}_{2}[μ-OH][BF\textsubscript{4}] \rightarrow \text{[Au(Pr)]}_{2}[μ-OH][BF\textsubscript{4}] \rightarrow \text{[Au(Pr)]}_{2}[μ-OH][BF\textsubscript{4}] \rightarrow \text{[Au(Pr)]}_{2}[μ-OH][BF\textsubscript{4}]
\end{equation}

Scheme 5. ([Au(Pr)]\_2[μ-OH][BF\textsubscript{4}]) with competing guest. (i) [Et\textsubscript{4}N][BF\textsubscript{4}] (25 mm).
Next we investigated whether it would be possible to switch the product selectivity during the course of the reaction (Figure 1). The reaction was initiated using only the dinuclear gold catalyst 2. Under these reaction conditions, the branched dimer 11 was the main product formed, indicating that the dual activation pathway is dominating. After 3 h, an excess of cage 1c was added, thereby removing the dinuclear gold complex from the reaction mixture by encapsulation of the cationic mononuclear gold fragment. The formation of 11 immediately stopped, while production of compound 10 started. After another 3 h, compound 7 was added as a competing guest for 1c, releasing the catalyst from the cage. As compound 10 can only be formed while the cationic gold species is encapsulated in 1c, its production stopped, whereas formation of 11 started again. The formation of product 12 followed the same trend as 11, but it was less clear as this compound was formed in much smaller amounts. As ketone 9 can be formed both inside and outside the cage (Table 1), the formation of this product could not be switched; the faster formation of this product after addition of both cage and Et₄N⁺BF₄⁻ (7) corresponds with the observations in Table 1.

In conclusion, we have demonstrated that it is possible to control the pathway by which gold complexes convert substrate molecules by complex encapsulation events. In the presence of a self-assembled hexameric resorcin[4]arene cage the dinuclear complex [{Au(NHC)}₂(μ-OH)][X] breaks into mononuclear units that are encapsulated as the dinuclear gold complex 2 is too large to fit inside the cage. By doing so, the dual activation reactivity typical for complex 2 is switched into (re)-activity that is typical for mononuclear complexes. By using this strategy on a reaction that can only proceed through a dual-activation pathway, we have demonstrated on/off switching of a gold-catalyzed reaction. Moreover, this approach also provides tools to change the product distribution during the course of a reaction, which is demonstrated in the activation of 4-phenyl-1-butyne. In summary, this strategy of switching the active species of a gold-catalyzed reaction by means of host-guest interactions provides a new approach to controlling catalytic transformations, even during the course of the reaction.

**Experimental Section**

**Hydrophenoxylation experiments:** The catalyst 2 (0.025 mol%) was added to a solution of 4 (550 mM) and 5 (500 mM) and in selected experiments cage 1c (50 mM) and/or competing guest 7 (50 mM) in [D₆]toluene. The mixture was heated to 80 °C and yields were monitored using GC and "H NMR of the crude mixture.

**Catalytic experiments with substrate 8:** The catalyst 2 (2.5 mol%), H₂O (44 mM), substrate 8 (66 mM), and, in selected experiments, cage 1c (33 mM) and/or competing guest 7 (33 mM) were mixed in [D₆]benzene and heated to 70 °C for 48 h. Yields were monitored using GC and "H NMR of the crude mixture and were determined as the average of two experiments.

**Acknowledgements**

Support for this work was generously provided by King Abdullah University of Science and Technology (KAUST) Office of Sponsored Research (OSR) under Award No. OSR-2015-CCF-


The fact that the reaction between diphenylacetylene and phenol does not take place in the presence of the cage could also be caused by the inability of the substrates and catalyst to coencapsulate inside the cage. However, the reaction between diphenylacetylene and thiophenol, which can be catalyzed by a mononuclear, α-activating catalyst due to the stronger nucleophile, did yield the coupling product. This shows that coencapsulation of the two substrates and the catalyst is possible and the hydrophenoxylation is switched off due to preventing the hydrophenols formation is switched off due to preventing the desired pathway. For references on hydrothiolation: a) X. Zhang, K. Wang, RSC Adv. 2015, 5, 34439–34446; b) T. Tamai, K. Fujiwara, S. Hiroshimae, A. Nomoto, A. Ogawa, Org. Lett. 2016, 18, 2114–2117.

