Angewandte
Highlights

Homogeneous Catalysis

DOI: 10.1002/anie.201307205

New Endeavors in Gold Catalysis—Size Matters**

Rafael Gramage-Doria and Joost N. H. Reek*

cluster compounds · gold · ligand effects ·
homogeneous catalysis · synthetic methods

The beginning of the 21st century witnessed an enormous increase in the number of research papers in which gold complexes were used in catalysis, and as such it is generally recognized as the start of this research area. It is, however, important to stress the pioneering work of the groups of Bond, Haruta, Hutchings, Ito, and Hayashi, work which in the 70s and 80s demonstrated that gold, long considered to be an inert metal, promoted some catalytic transformations and even induced some enantioselectivity in a few examples.[1] Although gold catalysis was initially focused on readily available gold(III) precursors ($NaAuCl_4$, $AuCl_3$, etc.), gold(I) species turned out to form the most active gold catalysts. This feature arises from the remarkable 6s orbital contraction and 5d orbital expansion (relativistic effects).[2a] The gold(I) oxidation state leads to a linear geometry about the gold(I) atom together with the additional ability to interact with other gold centers through d^{10}–d^{10} interactions, the distance of which can be as short as those found in hydrogen bonds.[2b] With easy access to gold(I) species, (in)organic chemists began explore the catalytic performance of various gold complexes with a variety of coordinated ligands (L) to tune the properties under homogeneous conditions.[3] Furthermore, the potential of gold catalysis was emphasized as it resulted in C–E bond-forming reactions (E = heteroatom) which were previously unknown, and had considerable utility as an easy entrance to molecular complexity. As is the case for many transition-metal-promoted reactions, phosphanes and more recently carbene ligands[4] were the ligands (L) considered for homogeneous gold(I) catalysis because of their versatility and accessibility. From the numerous studies that have appeared it is clear that the balance between the electronic and steric properties of the ligand to stabilize and enhance the activity of a gold catalyst is of utmost importance, therefore ligand screening is a viable tool in this field. The active gold species is usually prepared by addition of a halide scavenger to the LAuCl precatalyst complex, thus leading to a cationic gold species stabilized by a labile anion or a solvent molecule such as acetonitrile. Special mention is deserved for the fascinating results observed for heterogeneous catalysis promoted by well-defined gold nanoparticles and gold-supported materials.[5] Nowadays, gold catalysis is used in total synthesis (i.e. enabling shorter synthetic routes to target molecules)[6] as well as in reactions run on an industrial scale.[7] The large number of studies in the last 20 years on this topic have given rise to the discovery (sometimes by serendipity) of new organic reactions which can only be performed in the presence of a gold catalyst, and they have been extensively reviewed.[8] Additionally, an enormous amount of work devoted to gold catalysis has resulted in new concepts that might be required to address the challenges of the future. An original strategy regarding the design of gold(I) catalysts relies on encapsulating gold species. By taking advantage of host-guest chemistry, Raymond, Bergman, and Toste et al. have shown that catalyst stability and activity is enhanced upon encapsulation of a phosphine gold(I) catalyst in a water-soluble coordination cage.[9a] Furthermore, they have shown that such a cage-protected gold catalyst is suited for tandem reactions with enzyme catalysts because of the water solubility of the cage.[9b] Analogously, Scarso and Reek et al.,[10a] and Echavarren and Ballester et al.[10b] studied the encapsulation of carbene-based gold(I) complexes in self-assembled resorcarene cage structures and proved that catalyst selectivity can be controlled in a supramolecular fashion.[10c] Although tuning the catalyst activity through its second-sphere environment has been reported for other transition-metal catalysts, these examples represent a new tool for controlling the properties of gold catalysts beyond the ligand.

Two recent studies from the groups of Hashmi and Echavarren report yet another direction in homogeneous gold catalysis.[11] They both report approaches to generate nanosized catalysts by using either bulky groups attached to the gold complex, or the application of small gold clusters stabilized by ligands. The main advantage of Hashmi's catalysts is the high activity and stability, thus solving a drawback related to most of the homogeneous gold catalysts so far: the high catalyst loading (2 to 10 mol %) required. This result is clearly a major breakthrough for potential (industrial) applications of homogeneous gold catalysts. Hashmi et al. have designed an active gold catalyst which readily operates under homogeneous conditions with activity (TOF) and stability (TON) comparable to the best heterogeneous gold catalysts.[11a] They turned their attention to N-acyclic carbene

---

[*] Dr. R. Gramage-Doria, Prof. Dr. J. N. H. Reek
Van't Hoff Institute for Molecular Sciences
University of Amsterdam
Science Park 904, 1098 XH, Amsterdam (The Netherlands)
E-mail: r.gramagedoria@uva.nl
Homepage: http://www.science.uva.nl/research/imc/HomKat/

[**] Financial support was provided by the University of Amsterdam, The Netherlands Organization for Scientific Research-Chemical Sciences (NWO-CW), and the National Research School for Catalysis (NRSCC). The NWO is acknowledged for a Rubicon grant to R.G.-D.

gold complexes such as **1** (Figure 1). The carbene ligand of interest is functionalized with a bulky silsesquioxane unit remote from the gold center, which has a large influence on the catalytic properties of the carbene/gold complex. The ligand bearing the more sterically demanding substituents (R^1 = cyclooctyl, R^2 = 2,6-diethylphenyl) gave rise to the most active species for the synthesis of substituted phenols under homogeneous conditions [reaction (1) in Figure 1]. Actually, by using only 0.01 mol% of **1**, a TON of 5720 was observed, and the activity was also high (TOF of 18000 h^{-1}). In addition, a novel reaction was reported [reaction (2)] to be catalyzed by gold, also with impressive TON (32000000) and TOF (440000 h^{-1}) values. For this reaction only 10^{-6} mol% of the catalyst was required. Interestingly, comparison with a catalyst lacking the silsesquioxane moiety shows that the silsesquioxane cage is necessary to reach such unique activity and stability. This novel catalyst gives the highest activity ever reported for any gold catalyst.[5e]

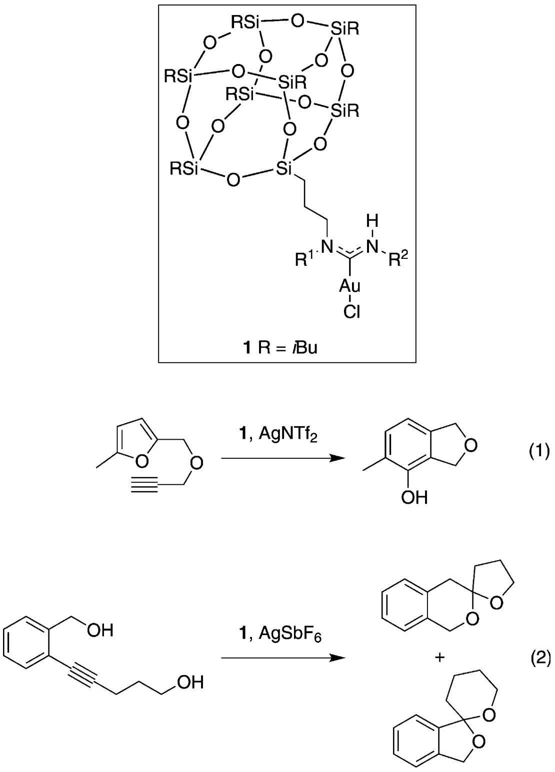

Figure 1. The silsesquioxane carbene catalyst **1** and its application in catalysis. Tf = trifluoromethanesulfonyl.

The other nanosized gold catalyst was reported by Echavarren et al.[11b] For several reasons, it has been accepted that ligand-based gold clusters were inactive in catalysis, in contrast to their mononuclear and naked analogues (gold nanoparticles). In the work reported by Echavarren et al., they show for the first time that a well-defined metal cluster comprising six gold atoms stabilized by only four phosphine ligands can be active in homogeneous catalysis (**2**; Figure 2). The gold cluster **2** can be regarded as a distorted square-planar bipyramid with four gold atoms in pseudoequatorial and two in pseudoapical positions (Au^a). All phosphorus (P) atoms and the four *ortho*-carbon (*o*-C) atoms are involved in coordination to the gold cluster. Surprisingly, **2** efficiently catalyzes the cycloaddition of the 1,6-enyne **3** and the [4+2] cycloaddition of **4** (Figure 2). It is claimed that the gold atoms in the apical position (Au^a), which have no coordinated phosphorus atoms, are the active sites responsible for the substrate activation. This claim is likely since these gold atoms are weakly stabilized by three-center-two-electron bonds, and therefore the substrates can easily compete for the coordination site. However, further proofs about the action mode of **2** will provide a better understanding of the active species. Importantly, they were able to fully recover the gold cluster **2** from the reaction mixture, thus demonstrating the stability of the catalyst under catalytic conditions. In addition, the large size of catalyst **2** compared to the products offers new opportunities for catalyst recycling by nanofiltration.[12] These findings clearly show a bright future for the fine-tuning and design of gold catalysts based on cluster species.

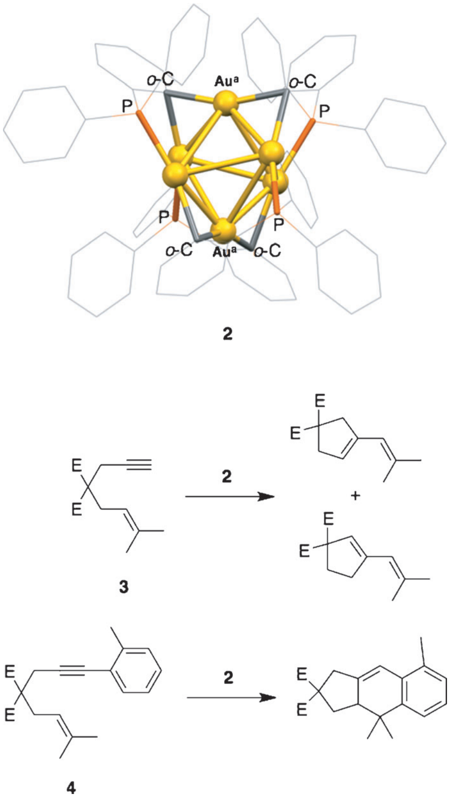

Figure 2. The cluster catalyst **2** and its application in catalysis. E = CO_2Me.

The results highlighted here are breakthroughs in gold catalysis and will serve as inspiration for the design of new catalytic systems and the applications to even more challenging reactions. It is therefore necessary to understand the activity and selectivity achieved by these complexes, especially the interesting effect of adjacent steric bulk, which may be beyond a ligand effect, a concept that possibly can be extended to other transition-metal catalysts. The demand for the development of new chemical transformations in industry, the design of environmentally friendly processes, and the creation of more active and selective catalysts will push the limits of transition-metal catalysis to a new level, and the examples highlighted herein are interesting steps in such a direction.

Received: August 16, 2013

---

[1] a) *Modern Gold Catalyzed Synthesis* (Eds: A. S. K. Hashmi, F. D. Toste), Wiley-VCH, Weinheim, **2012**; b) G. C. Bond, C. Louis, D. T. Thompson in *Catalytic Science Series*, *Vol. 6* (Ed.: G. H. Hutchings), World Scientific, Singapore, **2006**; c) A. S. K. Hashmi, G. J. Hutchings, *Angew. Chem.* **2006**, *118*, 8064–8105; *Angew. Chem. Int. Ed.* **2006**, *45*, 7896–7936.
[2] a) D. J. Gorin, F. D. Toste, *Nature* **2007**, *446*, 395–403; b) S. Sculfort, P. Braunstein, *Chem. Soc. Rev.* **2011**, *40*, 2741–2760.
[3] a) D. J. Gorin, B. D. Sherry, F. D. Toste, *Chem. Rev.* **2008**, *108*, 3351–3378; b) W. Wang, G. B. Hammond, B. Xu, *J. Am. Chem. Soc.* **2012**, *134*, 5697–5705; c) D. Wang, R. Cai, S. Sharma, J. Jirak, S. K. Thummanapelli, N. G. Akhmedov, H. Zhang, X. Liu, J. L. Petersen, X. Shi, *J. Am. Chem. Soc.* **2012**, *134*, 9012–9019.
[4] N. Marion, S. P. Nolan, *Chem. Soc. Rev.* **2008**, *37*, 1776–1782.
[5] a) D. I. Enache, J. K. Edwards, P. Landon, B. Solsona-Espriu, A. F. Carley, A. A. Herzing, M. Watanabe, C. J. Kiely, D. W. Knight, G. H. Hutchings, *Science* **2006**, *311*, 362–365; b) A. Corma, H. Garcia, *Chem. Soc. Rev.* **2008**, *37*, 2096–2126; c) A. A. Herzing, C. J. Kiely, A. F. Carley, P. Landon, G. J. Hutchings, *Science* **2008**, *321*, 1331–1335; d) Y. Zhang, X. Cui, F. Shi, Y. Deng, *Chem. Rev.* **2012**, *112*, 2467–2505; e) J. Oliver-Meseguer, J. R. Cabrero-Antonino, I. Dominguez, A. Leyva-Perez, A. Corma, *Science* **2012**, *338*, 1452–1455.
[6] a) A. Fürstner, P. W. Davies, *Angew. Chem.* **2007**, *119*, 3478–3519; *Angew. Chem. Int. Ed.* **2007**, *46*, 3410–3449; b) A. Fürstner, *Chem. Soc. Rev.* **2009**, *38*, 3208–3221; c) A. S. K. Hashmi, M. Rudolph, *Chem. Soc. Rev.* **2008**, *37*, 1766–1775; d) M. Rudolph, A. S. K. Hashmi, *Chem. Soc. Rev.* **2012**, *41*, 2448–2462.
[7] J. H. Teles, S. Brode, M. Chabanas, *Angew. Chem.* **1998**, *110*, 1475–1478; *Angew. Chem. Int. Ed.* **1998**, *37*, 1415–1418.
[8] a) A. S. K. Hashmi, *Angew. Chem.* **2010**, *122*, 5360–5369; *Angew. Chem. Int. Ed.* **2010**, *49*, 5232–5241; b) N. Krause, C. Winter, *Chem. Rev.* **2011**, *111*, 1994–2009; c) M. Rudolph, A. S. K. Hashmi, *Chem. Commun.* **2011**, *47*, 6536–6544; d) A. Corma, A. Leyva-Perez, M. J. Sabater, *Chem. Rev.* **2011**, *111*, 1657–1712; e) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Commun.* **2007**, 333–346; f) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180–3211; g) Z. Li, C. Brouwer, C. He, *Chem. Rev.* **2008**, *108*, 3239–3265; h) E. Jiménez-Núñez, A. N. Echavarren, *Chem. Rev.* **2008**, *108*, 3326–3350; i) A. Corma, A. Leyva-Perez, M. J. Sabater, *Chem. Rev.* **2011**, *111*, 1657–1712.
[9] a) Z. J. Wang, C. J. Brown, R. G. Bergman, K. N. Raymond, F. D. Toste, *J. Am. Chem. Soc.* **2011**, *133*, 7358–7360; b) Z. J. Wang, K. N. Clary, R. G. Bergman, K. N. Raymond, F. D. Toste, *Nat. Chem.* **2013**, *5*, 100–103.
[10] a) A. Cavarzan, A. Scarso, P. Sgarbossa,, G. Strukul, J. N. H. Reek, *J. Am. Chem. Soc.* **2011**, *133*, 2848–2851; b) L. Adriaenssens, A. Escribano-Cuesta, A. Homs, A. M. Echavarren, P. Ballester, *Eur. J. Org. Chem.* **2013**, 1494–1500; c) R. Gramage-Doria, R. Bellini, J. Rintjema, J. N. H. Reek, *ChemCatChem* **2013**, *5*, 1084–1087.
[11] a) M. C. Blanco Jaimes, C. R. N. Boehling, J. M. Serrano-Becerra, A. S. K. Hashmi, *Angew. Chem.* **2013**, *125*, 8121–8124; *Angew. Chem. Int. Ed.* **2013**, *52*, 7963–7966; b) E. S. Smirnova, A. M. Echavarren, *Angew. Chem.* **2013**, *125*, 9193–9196; *Angew. Chem. Int. Ed.* **2013**, *52*, 9023–9026.
[12] D. Astruc, F. Lu, J. R. Aranzaes, *Angew. Chem.* **2005**, *117*, 8062–8083; *Angew. Chem. Int. Ed.* **2005**, *44*, 7852–7872.