

FINAL ANALYSIS

Is Gold a Catalyst in Cross-Coupling Reactions in the Absence of Palladium?

In the last decade gold has emerged as a kind of “philosopher’s stone” in catalysis, being able to promote a bewildering variety of transformations, including cross-coupling reactions for the formation of carbon–carbon bonds. These highly useful transformations were developed in part by the 2010 Nobel Prize awardees Richard Heck, Ei-ichi Negishi and Akira Suzuki (1) and with contributions from many other research groups. Recently, there has been some question over whether gold can catalyse these reactions which have been traditionally catalysed by palladium complexes.

In 2007, Corma’s research group published a paper with the suggestive title ‘Catalysis by Gold(I) and Gold(III): A Parallelism between Homo- and Heterogeneous Catalysts for Copper-Free Sonogashira Cross-Coupling Reactions’ (2). This work stressed the similar behaviour of well-known homogeneous gold(I) complexes such as AuCl(PPh₃) with that of heterogeneous gold on ceria (Au/CeO₂) as catalysts for the Sonogashira coupling reaction. In addition to AuCl(PPh₃), a trinuclear Au(I) complex was also claimed to be a catalyst for this reaction (Scheme 1) (2–6). These homogeneous gold(I) catalysts were also reported to catalyse the Suzuki coupling of iodobenzenes with arylboronic acids (5, 6).

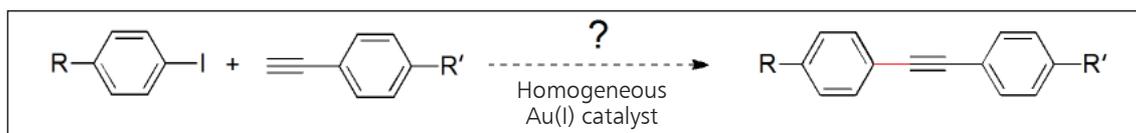
Traces of Palladium

Nevertheless, from a practical perspective, it is important to note that all these reactions proceeded only under much harsher conditions (130°C in *o*-xylene) (2–6) than those required with palladium catalysts.

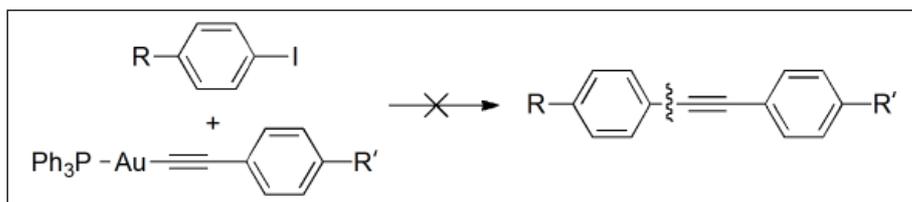
Moreover, only the most reactive iodobenzenes were used as the coupling partners. Another group reported that gold(I) iodide in the presence of mono- or diphosphines as ligands acted as a catalyst for the Sonogashira coupling of iodo- and activated bromobenzenes under similar conditions (130°C in toluene) (7).

A central argument behind the development of gold catalysts for cross-coupling chemistry was that “Au(I), having the same d¹⁰ configuration as Pd(0) can catalyse reactions typically catalysed by palladium” (2–6). However, this is a rather simplistic argument, since even elements within the same group often behave very differently in catalysis.

The first step in the catalytic cycle of haloarene coupling reactions is the oxidative addition of aryl halides (ArX) to the metal catalyst. Thus, for a gold-catalysed reaction of ArX with a catalyst AuX(L) (L = ligand), a square planar Au(III) complex AuArX₂(L) would be formed. There is no report for such oxidative addition. In fact, our preliminary results are pointing towards high activation barriers for these types of transformations and all our attempts to carry out the oxidative addition of a variety of iodobenzenes to AuCl(PPh₃) and other Au(I) complexes in a variety of solvents led to complete recovery of the starting materials (8). This is in sharp contrast to the behaviour of PdL₄ or Pd₂(dba)₃ + L systems, which react readily with aryl halides to give complexes PdArX(L)₂. Furthermore, we failed to observe any coupling reaction between iodobenzene and phenylacetylene catalysed by gold iodide and 1,2-(diphenylphosphino)ethane. Finally, we examined a possible Sonogashira coupling



Scheme 1. Can a homogeneous gold(I) complex catalyse the Sonogashira coupling reaction?



Scheme II. A gold(I) acetylide complex does not catalyse Sonogashira coupling

proceeding *via* a gold(I) acetylide (Scheme II), which also met with failure.

It has been reported that as little as 50 ppb Pd present in commercially available sodium carbonate is able to catalyse the Suzuki coupling reaction (9). Since high purity gold often contains traces of palladium, we suspected that palladium was actually responsible for the success of the Au(I)-catalysed 'Pd-free Sonogashira reaction'. Indeed, low loadings of palladium(0) were enough to carry out the couplings in Schemes I and II (8). Therefore, we concluded that it was very unlikely that gold(I) complexes alone could act as homogeneous catalysts for cross-coupling reactions of aryl halides and closely related organic substrates (Csp²-X containing electrophiles) (8).

Gold Nanoparticles

All of the previous discussion here pertains to coupling reactions catalysed under homogeneous conditions. However, we should also consider the possibility that the reaction proceeds *via* heterogeneous rather than homogeneous catalysis. We have previously shown that heterogeneous and homogeneous gold catalysts activate small molecules such as alkynes and alkenes by totally different mechanisms (10). Accordingly, it is not entirely surprising to find that gold nanoparticles are efficient catalysts for the Suzuki coupling reaction (11). The reaction catalysed by gold nanoparticles prepared from hydrogen tetrachloroaurate and 2-aminothiophenol proceeded satisfactorily using chlorobenzenes as substrates, which are less reactive than iodobenzene, under conditions (80°C, 4 h) much milder than those required with Au/CeO₂ (150°C, 24 h) in *o*-xylene (2–6).

In addition to contamination by palladium, which will depend on the particular source of gold used for the preparation of the gold complexes, is there any other way by which complexes like AuCl(PPh₃) could lead to species catalytically active in cross-coupling reactions? This issue was addressed last year by Lambert's group, which demonstrated that gold nanoparticles were formed as the active catalysts by the slow decomposition of the AuCl(PPh₃) complex

(12–14). Thus, in the reaction between iodobenzene and phenylacetylene, long induction periods (145°C, 100 h) were required to detect the Sonogashira coupling product in low yield.

Corma's group has recently published results that further confirm the active role of gold nanoparticles in cross-coupling reactions, along with theoretical calculations that support the unlikelihood of a homogeneous Au(I)-catalysed Sonogashira coupling reaction (15), in line with our own conclusions (8).

Conclusions

Taken together, all these results show that fundamental differences exist between heterogeneous and homogeneous catalysts (10). In order to bridge the gap between these two fields, a deeper understanding of catalytic systems and their active species is required.

Thus, while gold nanoparticles may play a role in catalysing cross-coupling reactions, homogeneous gold(I) complexes are unlikely to act as catalysts for these reactions in the absence of palladium.

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References

- 1 'Scientific Background on the Nobel Prize in Chemistry 2010: Palladium-Catalyzed Cross Couplings in Organic Synthesis', The Royal Swedish Academy of Sciences, Stockholm, Sweden, 6th October, 2010: http://nobelprize.org/nobel_prizes/chemistry/laureates/2010/sci.html (Accessed on 18th May 2011)
- 2 C. González-Arellano, A. Abad, A. Corma, H. García, M. Iglesias and F. Sánchez, *Angew. Chem. Int. Ed.*, 2007, **46**, (9), 1536
- 3 C. González-Arellano, A. Corma, M. Iglesias and F. Sánchez, *Eur. J. Inorg. Chem.*, 2008, (7), 1107
- 4 A. Corma, C. González-Arellano, M. Iglesias, S. Pérez-Ferreras and F. Sánchez, *Synlett*, 2007, (11), 1771

- 5 C. González-Arellano, A. Corma, M. Iglesias and F. Sánchez, *J. Catal.*, 2006, **238**, (2), 497
- 6 A. Corma, E. Gutiérrez-Puebla, M. Iglesias, A. Monge, S. Pérez-Ferreras and F. Sánchez, *Adv. Synth. Catal.*, 2006, **348**, (14), 1899
- 7 P. Li, L. Wang, M. Wang and F. You, *Eur. J. Org. Chem.*, 2008, (35), 5946
- 8 T. Lauterbach, M. Livendahl, A. Rosellón, P. Espinet and A. M. Echavarren, *Org. Lett.*, 2010, **12**, (13), 3006
- 9 R. K. Arvela, N. E. Leadbeater, M. S. Sangi, V. A. Williams, P. Granados and R. D. Singer, *J. Org. Chem.*, 2005, **70**, (1), 161
- 10 M. García-Mota, N. Cabello, F. Maseras, A. M. Echavarren, J. Pérez-Ramírez and N. López, *ChemPhysChem*, 2008, **9**, (11), 1624
- 11 J. Han, Y. Liu and R. Guo, *J. Am. Chem. Soc.*, 2009, **131**, (6), 2060
- 12 G. Kyriakou, S. K. Beaumont, S. M. Humphrey, C. Antonetti and R. M. Lambert, *ChemCatChem*, 2010, **2**, (11), 1444
- 13 V. K. Kanuru, G. Kyriakou, S. K. Beaumont, A. C. Papageorgiou, D. J. Watson and R. M. Lambert, *J. Am. Chem. Soc.*, 2010, **132**, (23), 8081
- 14 S. K. Beaumont, G. Kyriakou and R. M. Lambert, *J. Am. Chem. Soc.*, 2010, **132**, (35), 12246
- 15 A. Corma, R. Juárez, M. Boronat, F. Sánchez, M. Iglesias and H. García, *Chem. Commun.*, 2010, **47**, (5), 1446

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