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# On the Mechanism of the Digold(I) Hydroxide-Catalyzed Hydrophenoxylation of Alkynes

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Dedicated to the memory of our friend and colleague Professor Tom Ziegler

Abstract: Herein we present a detailed investigation of the mechanistic aspects of the dual gold-catalysed hydrophenoxylation of alkynes, using both experimental and computational methods. The dissociation of [{Au(NHC)}\_2(\mu-OH)][BF\_4] is essential to enter the catalytic cycle; this step is favored in the presence of bulky, non-coordinating counterions. Moreover, in silico studies confirmed that phenol does not only act as a reactant, but as a co-catalyst, lowering the energy barriers for several transition states. A gem-diaurated species might form during the reaction, but this lies deep within a potential energy well, and is likely to be an 'off-cycle' rather than an 'in-cycle' intermediate.

#### Introduction

The end of the 20th and the beginning of the 21st century saw the advent of a veritable "gold rush".<sup>[1]</sup> With this was associated a sizeable number of publications dealing with the stoichiometric and catalytic reactivity of gold.<sup>[2]</sup> The main driving force behind this modern gold fever was the discovery that gold salts and complexes could catalyse a wide range of chemical reactions, despite the longstanding dogma of inertness held throughout the ages.<sup>[3]</sup> It has been

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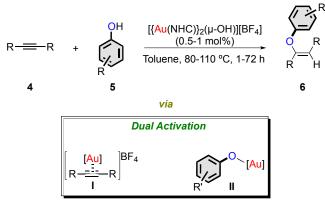
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Supporting information for this article is given via a link at the end of the document, kinetic studies details, characterization data for all the compounds, computational details, and Cartesian coordinates.

assumed that all gold-mediated transformations proceeded through the interaction of one gold centre with one substrate, until the seminal work of Toste and Houk in 2008. [4] In this report, it was proposed that not one but two gold centres could interact with one substrate, thereby generating  $\sigma,\pi$ -digold acetylide or *gem*-diaurated species. Since then, several research groups have contributed to our understanding of these diaurated complexes and their role in catalysis, [5] enabling the development of novel gold-catalysed transformations that require dual activation of the substrate by the gold catalyst. Specific catalysts for dual activation processes have also been developed as a result of this seminal work. [6]

The Nolan group has reported the synthesis and reactivity studies of a series of diaurated complexes of the formula  $[{Au(NHC)}_2(\mu\text{-OH})][BF_4]$  (1-BF<sub>4</sub>)<sup>[7,8]</sup> and their use as catalysts for alkyne hydrophenoxylation.<sup>[9]</sup> Phenols are more acidic than most aliphatic alcohols, and until recently the only protocol for their gold-catalysed addition to alkynes relied upon high catalyst loadings, temperatures and reaction times, and produced only moderate yields.<sup>[10]</sup> In contrast, the addition of aliphatic alcohols to alkynes has been well-known for a number of years.<sup>[11]</sup>

Digold hydroxides **1** can be considered as a combination of a Lewis acid [Au(NHC)][BF<sub>4</sub>] (**2**) and a Brønsted base [Au(OH)(NHC)] (**3**). Preliminary mechanistic studies suggested that the hydrophenoxylation reaction proceeded via a dual activation mechanism, whereby the [Au(NHC)][BF<sub>4</sub>] (**2**) fragment coordinates to the alkyne (**4**) to form gold-alkyne  $\pi$ -complex **I** and [Au(OH)(NHC)] (**3**) deprotonates the phenol (**5**) to generate gold phenoxide  $\mathbf{II}^{[12]}$  (Scheme 1). The product is a *Z*-vinyl ether (**6**).



Scheme 1. Hydrophenoxylation of alkynes *via* dual activation.

This reaction represents the first example of two gold centres interacting independently with two substrates to generate activated species that react in an intermolecular fashion.

The typical mechanistic scenario for the gold-catalysed addition of nucleophiles to alkynes involves activation of the alkyne by cationic gold followed by outer-sphere antiperiplanar attack of the alkyne by the nucleophile, [14] with concomitant slippage of the gold centre to the other carbon atom. [15,16] In contrast, our hydrophenoxylation reaction requires that the phenol nucleophile first be activated as a gold phenoxide complex, which then reacts with the gold-alkyne complex. The mechanism of these reactions was recently discussed in depth in a recent study by Maier and co-workers. [16] They suggested that our protocol is a rare exception that does not follow the typical catalytic cycle previously investigated in the study of gold chemistry. [17]

Therefore, we sought to explore the mechanistic aspects of this exciting and intriguing reaction, to fully understand the implications for gold catalysis. We have relied heavily on DFT calculations; while these were challenging to carry out on systems of this size, they have allowed previously unseen levels of insight into dual catalysis mechanism. Supporting experimental work was carried out to explore key steps and processes.

At the outset, answers to several key questions were sought:

- Does the reaction proceed via dissociation of the digold hydroxide species as suggested in Scheme 1?
- Is a digold phenoxide species (III) involved in the reaction?
- Are gem-diaurated intermediates involved in this reaction?
- What is the role of water?

With these studies we have sought to contribute to the understanding of the interactions involved in dual-gold-catalysed reactions, and anticipate that this information will help design more efficient dual activation protocols.

#### **Results and Discussion**

Initial studies<sup>[9]</sup> confirmed that the dissociation/reassociation of **1** occurs rapidly. A mixture of [{Au(IPr)}<sub>2</sub>( $\mu$ -OH)][BF<sub>4</sub>] (**1a**-BF<sub>4</sub>) and [{Au(SIPr)}<sub>2</sub>( $\mu$ -OH)][BF<sub>4</sub>] (**1b**-BF<sub>4</sub>) rapidly equilibrates to a 1:2:1 mixture of **1a**-BF<sub>4</sub>, [{Au(IPr)}( $\mu$ -OH){Au(SIPr)}[BF<sub>4</sub>] (**1c**-BF<sub>4</sub>) and **1b**-BF<sub>4</sub> (eq. 1). Complexes **I** are poorly reactive with phenol,

and complexes II are poorly reactive with alkyne (eq. 2 and 3).

$$\begin{bmatrix} Au(|Pr) \\ Ph \stackrel{-}{=} Ph \end{bmatrix}^{+} + \underbrace{\downarrow}_{5} \stackrel{OH}{Anhydrous} \stackrel{Ph}{\downarrow}_{H} \stackrel{Ph}{\downarrow}_{6} (8\%)$$

$$(2)$$

$$Au(|Pr) + Ph \stackrel{Ph}{=} Ph \xrightarrow{Anhydrous} 6 (3)$$

$$Anhydrous$$

Moreover, I and II successfully react to re-form 1 and deliver the product (Scheme 2). [9] However, a *gem*-diaurated species (IV) was observed by NMR spectroscopy when this was carried out under anhydrous conditions.

$$\begin{bmatrix} Au(|Pr) \\ Ph \xrightarrow{---} Ph \end{bmatrix}^{+} + \begin{bmatrix} Au(|Pr) \\ I \end{bmatrix}$$

$$Anhydrous$$

$$\begin{bmatrix} Anhydrous \\ Anhydrous \end{bmatrix}^{+} + \begin{bmatrix} Au(|Pr) \\ I \end{bmatrix}^{+} + \begin{bmatrix} Au(|Pr) \\ I$$

Scheme 2. Preliminary mechanistic studies.

With these initial results in mind, it was then logical to expect that an inner-sphere counterion (such as OTf or NTf<sub>2</sub>) might reduce reactivity compared to more weakly coordinating counter-ions such as  $BF_4$ , FABA and  $SbF_6$  (FABA = tetrakis(pentafluorophenyl)borate). Kinetic experiments conducted using a model reaction (the hydrophenoxylation of diphenylacetylene with phenol; monitored by GC-FID) confirmed that the reactivity of [{Au(IPr)}2(µ-OH)][X] decreased in the order  $X = SbF_6 \approx BF_4 \approx FABA > OTf >> NTf_2$ , supporting our hypothesis (see the Supporting Information for profiles).[18] This is in direct contrast with recent reports on the counterion effect on gold-catalysed hydroalkoxylation of alkynes. There the counterion plays a crucial role in stabilizing key intermediates and aiding the protodeauration step, acting as a proton shuttle. This supports the hypothesis that our reaction does not follow a prototypical gold catalytic cycle, and instead proceeds via the reaction of phenoxide II with gold-alkyne complex I.[19] These results are supported by DFT calculations that show that the dissociation of BF<sub>4</sub> from the cationic moiety [Au]<sup>+</sup> is facile, bearing in mind the binding energy of NTf2 is 17.6 kcal/mol stronger.

Previous studies have shown that  ${\bf 1a}$  reacts with phenol to form  $[\{Au(IPr)\}_2(\mu\text{-OPh})]$  ( ${\bf III}$ ). The need for a dissociative pathway raises questions regarding the possible involvement of a digold phenoxide complex, particularly as the reaction proceeds in the presence of a large excess of phenol with respect to  ${\bf 1}$ . Complex  ${\bf III}$  could be prepared and isolated under rigorously anhydrous conditions, and was characterised by NMR spectroscopy, elemental analysis, and crystallographic methods (see

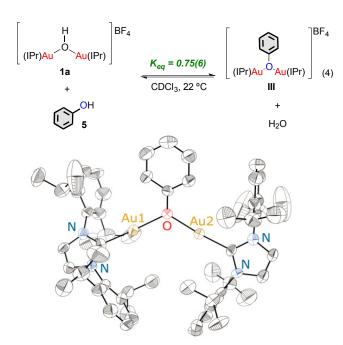


Figure 1. X-ray crystal structure of digold phenoxide III (cationic part).

Figure 1). The X-ray crystal structure confirms the structure of this intermediate, which is air- and moisture sensitive and decomposes to yield digold hydroxide and phenol under ambient conditions.

NMR experiments conducted by exposing 1a-BF4 to different concentrations of phenol (in CDCl3, using 1,3,5trimethoxybenzene as an internal standard) allowed the equilibrium constant for the formation of III from 1a to be calculated ( $K_{eq} = 0.75 \pm 0.06$  at 295 K) (eq. 4). This equilibrium constant suggests that, in the presence of 220 equiv. phenol under catalytic conditions, the major species will be III; the reactivity of this species must therefore be considered (vide infra). Hydrophenoxylation reactions carried out under anhydrous conditions were slightly slower than those carried out using technical grade toluene. This suggests that water assists one or more steps of the mechanism. In addition, reactions using III as the catalyst, under anhydrous conditions (to avoid in situ formation of 1a) were found to occur at a rate ca. 75% of that of the reaction catalysed by 1a (see the ESI). Phenol and water both play a dual role: they are involved in the equilibrium between 1a and III. and provide a proton source for the protodeauration step.[20]

We were concerned that water could also act as a nucleophile, forming the corresponding ketone side product from the hydration of the alkyne, thus reducing the efficiency of the process or leading to purification issues. [21] Since digold-hydroxides 1 have also proven to be very active catalysts for alkyne hydration, [22] we were surprised to observe no formation of ketone side-products under our standard conditions in technical grade toluene. Intrigued by this, we probed the effect of water on the hydrophenoxylation reaction. Water was accurately added to the reaction media (0.5, 1, 2, 5 and 8 equiv. with respect

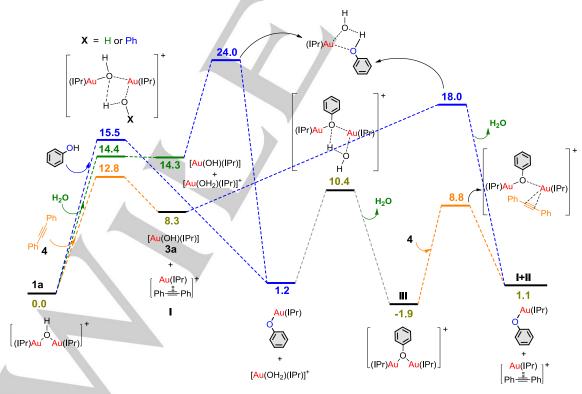


Figure 2. Computed stationary points of the reaction pathways linking 1a catalyst with I + II, using 4a as a substrate (Gibbs free energies (G) are given in kcal/mol).

to phenol) and the conversion to the final product was followed by GD-FID. While the conversions decreased when water was added, no formation of the expected ketone, or any other side products, could be observed. [23] This suggests that the hydrophenoxylation is favored versus the hydration process under our reaction conditions. Hydration reactions are most often carried out in polar, water-miscible solvents, such as methanol or 1,4dioxane,[24] while the poor miscibility of toluene and water will preclude the presence of high concentrations of water. In the experiments we carried out a biphasic system was observed when significant quantities of water were added. Nevertheless, there is clearly also a deleterious effect of water at higher concentrations, which might be due to perturbation of the equilibrium in equation 4, or the sequestration of cationic gold species as aqua complexes. Furthermore, we also conducted experiments with PhOH-d<sub>6</sub> but these were unfortunately inconclusive, with deuterium incorporation at various positions.

Finally, we attempted to isolate the postulated *gem*-diaurated species **IV** by mixing intermediates **I** and **II** in the presence of excess alkyne, under an inert atmosphere and anhydrous conditions. While NMR signals for a new species were observed and tentatively assigned to the desired diaurated compound, attempts to isolate and/or crystallize this species were unsuccessful. When the excess diphenylacetylene was removed, the starting materials were recovered, suggesting reversible C-O bond formation. <sup>[9]</sup> As we found ourselves at the limit of what we could study experimentally, we turned to DFT calculations for assistance.

Despite the considerable size of the systems when dealing with two gold-NHC moieties, we used density functional theory (DFT) calculations to investigate the proposed reaction mechanism in detail using [{Au(IPr)}2(µ-OH)][BF<sub>4</sub>] (1a-BF<sub>4</sub>) as the catalyst, diphenylacetylene (4) as a substrate and phenol (5) as a nucleophile. Figure 2 presents the computed reaction energy profile for the formation of I and II from 1a via three different pathways. The calculations start from the X-ray characterised hydroxide-bridged digold species 1a with  $BF_4$  as the counterion. In solution, even though past experiments outline an active role for counterions,[18,19] particularly in assisting the formation of the vinyl gold intermediate, here computationally any favourable interaction between 1a and BF<sub>4</sub> is lost, since completely separated **1a** and BF<sub>4</sub> is 4.2 kcal/mol lower in energy.

We have thoroughly checked the potential role of BF<sub>4</sub><sup>-</sup> in the subsequent catalytic steps, but the non-coordinating character did not suggest that any of these steps are assisted by the counterion.<sup>[20]</sup> Even though we considered the reaction starting from 1a, the digold phenoxide III is achieved after two steps (see Figure 2), and the upper barrier of this pathway (15.5 kcal/mol) corresponds to the cleavage of 1a by phenol. The latter may be the most likely mechanism but we cannot rule out the cleavage of 1a by alkyne or water. However, cleavage by the latter is unlikely due to the lower concentration of water in solution together with the fact that the upper barrier to obtain species I and II

is 24.0 kcal/mol (with respect to **1a**) despite displaying a barrier 1.1 kcal/mol lower for the cleavage of **1a**, compared to phenol. Experimental results suggest that the digold species (**1a**) and alkyne (**4**) are in equilibrium with the alkyne  $\pi$ -complex (**I**) and monogold hydroxide (**3a**) (Eq. 5) [9]

$$\begin{bmatrix} H \\ (IPr)Au \overset{O}{O} & Au(IPr) \end{bmatrix}^{BF_4} + \begin{bmatrix} Ph \\ Ph \end{bmatrix} & --- & \begin{bmatrix} Au(IPr) \\ Ph & Ph \end{bmatrix}^{BF_4} + \begin{bmatrix} Au(OH)(IPr) \end{bmatrix} (5)$$
1a 4 | 3a

According to calculations, this equilibrium is displaced towards 1a and 4a by 8.3 kcal/mol, thus it seems reasonable to assume that under the reaction conditions (i.e. a large excess of the alkyne with respect to the catalyst), appreciable quantities of I and 3a would be present. With this framework in mind, the digold species 1a can be broken into the two monogold species I and I and I overcoming a barrier of I and I section I and I in the hydroxy group of I and I in the hydroxy group of I and I in the hydroxy group and I i

Having addressed the formation of the monogold species I and II, we can now describe the catalytic cycle (see Figure 3a). The starting point is the nucleophilic attack of the alkyne ligand of I by phenoxide II resulting in the formation of a stable diaurated intermediate IV. Intermediate IV lies just 0.6 kcal/mol in energy above I + II and requires overcoming a barrier of 15.2 kcal/mol. From IV, there are four possible pathways for release of the vinylgold species: either reaction with phenol, water, or alkyne (to form the corresponding phenol, aqua or alkyne complexes), or by formation of a gem-diaurated species V (Figure 3).[25] The concentrations of these species that will be present will depend on the reaction conditions and on the degree of conversion; i.e. at high conversion the concentration of alkyne will be low. The transition state IV-V located for the formation of the gem-diaurated species V is depicted in Figure 4 as well as the transition state IV-VI for removal of the cationic gold fragment using a molecule of water. Notably, gemdiaurated species have recently been widely implicated in gold catalysis, although it is not always clear whether they are oncycle or off-cycle intermediates.[26] Even though V lies 9.5 kcal/mol below IV and requires a barrier of only 8.1 kcal/mol to be overcome, the barrier for reaction of IV with water to form VI directly is lower.

Moreover, reactions of **IV** with either phenol or alkyne are both energetically competitive with *gem*-diaurated species formation, differentiated by 0.8 and 1.2 kcal/mol, respectively. In this context, and particularly due to the deep potential energy well in which **V** sits and the large excess of both phenol and alkyne, the direct formation of vinyl-gold intermediate **VI** seems much more likely for operational catalytic turnover, whereas *gem*-diaurated species are expected to be *off-cycle* intermediates in this reaction. However, at higher conversions (i.e. lower concentrations of alkyne and phenol), the formation of *gem*-diaurated species might become competitive.

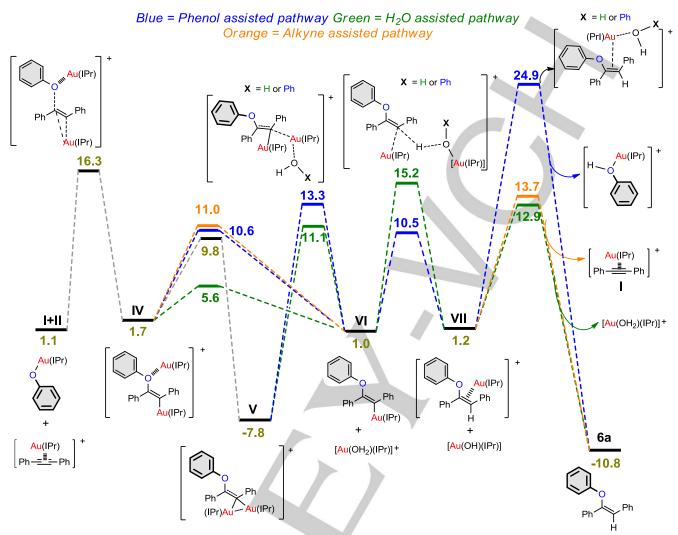


Figure 3. a) Computed stationary points for the dual-gold-catalyzed hydrophenoxylation using 4 as a substrate, 5 as a nucleophile, from the metal catalytic combination I+II (Gibbs free energies are given in kcal/mol).

Subsequent protodeauration, assisted by phenol, delivers the enol-ether species **VII** and regenerates gold-phenoxide **I**; if water were to perform this role the barrier is higher and the corresponding hydroxide would be produced, which can re-enter the cycle by reaction with phenol. The final decomplexation of the gold in **VII** can be achieved by reaction with alkyne or water. The former will directly regenerate gold-alkyne complex **I**, while the latter will form a gold-aqua complex that would react with **II** forming digold-phenoxide **III** overcoming a barrier of 9.2 kcal/mol, and then dissociate in the presence of alkyne requiring 10.7 kcal/mol to deliver **I** + **II** and thus re-enter the catalytic cycle (see Figure 2).

For the sake of a broader analysis and to unravel why experimentally the hydrophenoxylation of **4a** gives only the trans-product **6**, we explored the possible reaction pathway to generate the cis-isomer **6cis**. However, our results showed that this pathway contains intermediates that are either endothermic in nature or they are connected by high-energy barriers (see

Figure S1 in the Supporting Information). The main results can be summarized as follows: the predicted barriers for the formation of intermediates **IVcis** and **Vcis** are 6.5 and 27.6 kcal/mol higher in energy (respectively) when compared to the barriers for their trans counterparts (intermediate **IV** and **V**) given in Figure 3a.

A key question is this: why do not mono-gold catalysts mediate this reaction? To explore this, calculations were also carry out to unravel any potential mono-gold reaction pathway. The most preferred one displays a barrier for the C···O bond formation between the alkyne and the phenoxide moieties placed at 42.8 kcal/mol above 1a, to be compared with the barrier described by the transition state I+II→IV, which is 26.5 kcal/mol lower in energy (see Figure 3), and pointing out that this monogold alternative pathway would not drive to the 6, but to the 6-cis. The high barriers that a monogold-catalysed process would have to overcome are evident from, and consistent with, the very forcing conditions that Sahoo and coworkers required to conduct this reaction with AuCl<sub>3</sub>.<sup>[10]</sup>

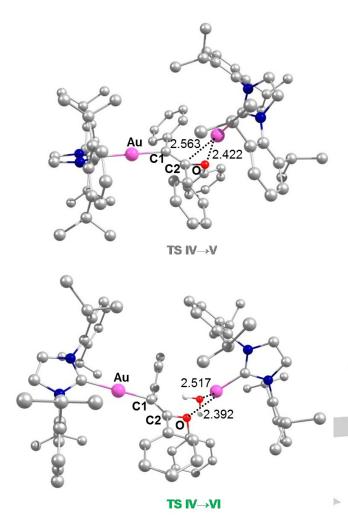


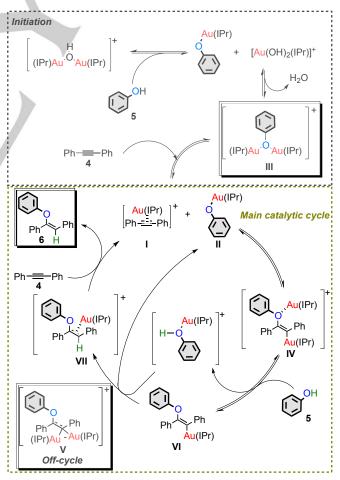
Figure 4. Molecular structures of computed transition states linking intermediates IV with V and VI. Selected distances are indicated in Å.

#### **Computational Details**

All the DFT static calculations have been performed at the GGA level with the Gaussian09 set of programs, [27] using the BP86 functional of Becke and Perdew.[28] The electronic configuration of the molecular systems was described with the standard split-valence basis set with a polarization function of Ahlrichs and co-workers for H, C, N, and O (SVP keyword in Gaussian).[29] For Au we used the quasi-relativistic Stuttgart/Dresden effective core potential, with the associated valence basis set (standard SDD keywords in Gaussian09).[30] The geometry optimizations were carried out without symmetry constraints, and the characterization of the stationary points was performed by analytical frequency calculations. Single point calculations on the BP86 optimized geometries were performed using the M06 functional<sup>[31]</sup> with the triple- $\zeta$  basis set of Ahlrichs for main-group atoms (TZVP keyword in Gaussian),[32] while for Au the SDD basis set has been employed. These single point calculations also used the polarizable continuous model PCM to model the solvent effects, using toluene as a solvent.[33] The reported free energies in this work include energies obtained at the M06/TZVP level corrected with zero-point energies, thermal corrections and entropy effects evaluated at 298 K and 1354 atm<sup>[34]</sup> with the BP86/SVP method in the gas phase.

#### **Conclusions**

In conclusion, a series of in silico studies, supported by experimental work, have been carried out to further elucidate mechanistic aspects of the hydrophenoxylation of alkynes. The results suggest that the synergic cooperation of two monogold species facilitates this process, while analogous mono-gold species are not capable of mediating this reaction. All insights, both experimental and theoretical, support the proposed dual activation pathway for this transformation (see Scheme 3). There is a considerable counter-ion effect, with more coordinating counter-ions reducing the rate of reaction. The dissociation of the digold species via three possible mechanisms was explored (alkyne, water, phenol) confirming that this process is essential to enter the catalytic cycle. Even though the digold-phenoxide species III only has an active role before the catalytic cycle, it is a sine qua non precursor of the active catalytic species.



Scheme 3. Hydrophenoxylation of alkynes via dual gold activation catalysis.

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However, the oft-mentioned gem-diaurated species are unlikely to play a role in this reaction; competing processes mediated by water, phenol and alkyne serve to disfavour the formation of such a complex, which lies in a very deep potential energy well and is unlikely to contribute to productive catalysis. Finally, water is shown to have a key role.

With these studies we have sought to explore and explain the most likely interactions involved in dual-gold-catalysed reactions, and anticipate that this information will help in the design of more efficient dual activation protocols. We are currently studying the use of digold hydroxide species in other dual-goldcatalysed reactions and these results will be published in due course.

#### **Acknowledgements**

The ERC (Advanced Investigator Award-FUNCAT), EPSRC and Syngenta are gratefully acknowledged for support. Umicore AG is acknowledged for their generous gift of materials. S.P.N. and L.C. thank King Abdullah University of Science and Technology (CCF project) for support. Y.O. thanks the Uehara Memorial Foundation for a Research Fellowship. A.P. thanks the Spanish MINECO for a project CTQ2014-59832-JIN, FEDER grant UNGI10-4E-801, and European Commission for a Career Integration Grant (CIG09-GA-2011-293900).

NHC, Abbreviations: FABA, N-heterocylic carbene; IPr. tetrakis(pentafluorophenyl)borate; 1,3-bis(2,6diisopropylphenyl)imidazol-2-ylidene; SIPr, 1,3-bis(2,6diisopropyl-phenyl)imidazolidine

Keywords: homogeneous catalysis • kinetic studies • DFT calculations • dual catalysis • gold catalysis • alkyne • hydrophenoxylation

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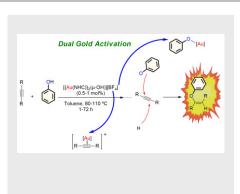
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### COMMUNICATION

Hydroarylation of alkynes mediated by gold centers occurs via a bimetallic cooperative mechanism.



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